Archives of Neurology and Psychiatry

VOLUME 48 SEPTEMBER 1942 NUMBER 3

EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

III. STUDIES IN SENSATION

LAURENCE M. WEINBERGER, M.D.*
Adjunct Neurosurgeon, Michael Reese Hospital
CHICAGO
AND
FRANCIS C. GRANT, M.D.
PHILADELPHIA

The new operation of intramedullary tractotomy (Sjöqvist) has reawakened an interest in the anatomic arrangement and physiologic functions of the fibers composing the descending tract of the trigeminal nerve. Current ideas on these matters have been derived largely from clinicopathologic observations in cases of thrombosis of the posterior inferior cerebellar artery and of syringobulbia in which the intramedullary trigeminal fibers were involved in the pathologic process. Lesions of this character, because of their irregular size and intensity of destruction, have obvious disadvantages when a study of the clinical effects relating to impairment of a single structure or of an isolated tract is desired. Surgical transection of the descending tract of the trigeminal nerve in man, performed by means of a small controlled incision into the tuberculum cinereum, obviates many of the former difficulties and allows for the first time correlation of sensory changes with a small lesion accurately placed in the descending tract.

MATERIAL

The material to be presented was derived from quantitative sensory studies of the face following intramedullary tractotomy. Of the 20 cases in which operation was performed, the results of sensory tests in 18 are considered in detail in this communication. In 1 case detailed examinations were impossible, and in 1 no sensory alterations were apparent after operation.

Of the 20 cases, operation in 8 was performed for the relief of major trigeminal neuralgia. In 12 cases intractable pain due to malignant disease about the face served as the surgical indication. In the second group death prevented an opportunity to study the late sensory changes, but adequate follow-up sensory

* Late Charles Harrison Frazier Fellow in Neurosurgery at the Hospital of the University of Pennsylvania.

This material is presented from the Neurosurgical Service of the Hospital of the University of Pennsylvania.

examinations were obtained in the group with trigeminal neuralgia at periods ranging from five and a half weeks to twenty months after operation.

After presentation of the results of sensory studies, the anatomic and physiologic problems concerning the trigeminal tract will be discussed in the light of the information gained in these studies. The conclusions respecting the applicability of intramedullary tractotomy to the relief of facial pain, so far as they are related to the production of facial analgesia, will also be considered in the appropriate section. The present paper amplifies and elaborates on an earlier report from this clinic.[1]

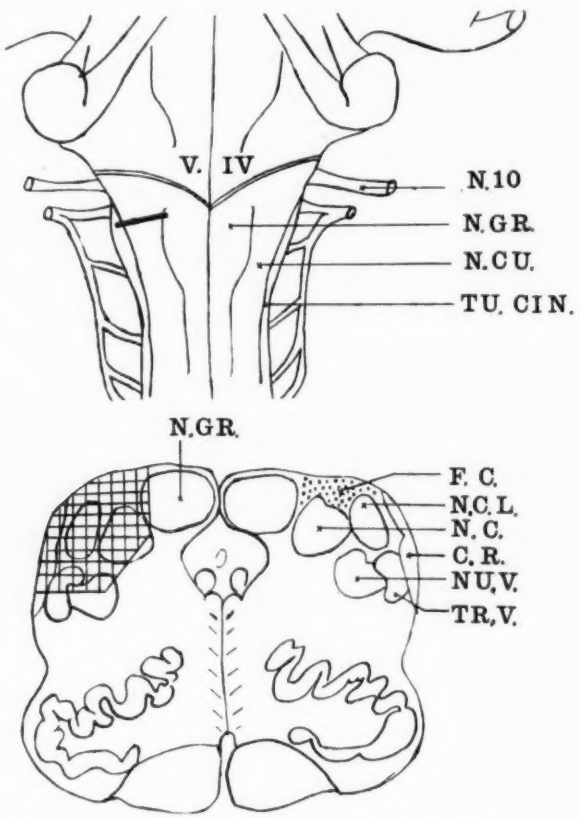

Fig. 1.—An outline drawing of the dorsal surface of the medulla, showing the tractotomy incision cutting across the cuneate nucleus and fasciculus. The cross sectional sketch at this level shows the approximate depth and extent of the incision and the structures implicated. The following abbreviations are used: *C. R.*, corpus restiforme; *F. C.*, fasciculus cuneatus; *N. CU.*, nucleus cuneatus; *N. C. L.*, nucleus cuneatus lateralis; *N. GR.*, nucleus gracilis; *N. 10*, vagus nerve; *NU. V.*, spinal nucleus of the trigeminal nerve; *TR. V.*, descending tract of trigeminal nerve; *Tu. Cin.*, tuberculum cinereum; *V. IV.*, fourth ventricle.

1. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Root of the Fifth Cranial Nerve, Arch. Neurol. & Psychiat. **43**:498 (March) 1940.

METHODS OF EXAMINATION

All but a few patients were studied with graduated von Frey thorns and hairs.[2] When gross testing was done, it is so indicated on the sensory charts. In every instance it was possible to examine pain sensation with graduated thorns. This was less difficult than testing touch sensitivity with hairs, because in tests for the latter modality better cooperation and a keener discriminatory faculty are demanded of the patient. All our conclusions, however, concerning the sensation of touch are based only on results in those cases in which graduated hairs were used. The methods of examination applied in the previous and in the present study are part of the plan of standard sensory examination introduced into this clinic by Dr. F. H. Lewy.

Pain Sensation.—Three or four areas within each trigeminal division were examined separately with graduated thorns, starting with a 1 Gm. thorn and increasing the strength of the thorns until the patient perceived a "sharp" sensation. If no such response was obtained by using the strongest thorn in our set (20 Gm.), a spring algesiometer (Head algesiometer) was resorted to, which graduated pressures up to 40 Gm. Insensitivity to pressure of more than 40 Gm. was considered for all practical purposes as complete analgesia. When a given threshold was found its extent was marked out on the face. In the accompanying sensory charts the numeral 40 with a line drawn through it thus, 4/0, means that the area was insensitive to pressures of 40 Gm. or more with the algesiometer. Otherwise the numerals represent the thresholds of pain appreciation expressed in grams. The normal thresholds for pain perception range from 0.25 to 1.0 Gm. Unless otherwise stated on the sensory chart or in the protocols, the threshold on the intact side of the face was within normal limits. For the sake of convenience, all the sensory charts show the right side of the face, but the side actually examined is stated in the protocols.

Touch Sensation.—Touch sensation was studied with respect to (1) the number of touch points per square centimeter of skin area and (2) the threshold of touch sensation for the touch points present. With a rubber stamp, several areas of 1 sq. cm. were marked out on the skin in each of the three trigeminal divisions. The number of touch points within each inked square was determined by systematic exploration, with the lightest hair that could be perceived. As each touch point was discovered, its location was marked with an ink spot. Thus the number of touch points per square centimeter was determined, the threshold stimulus being used. In several instances in which the number of touch points per square centimeter was much reduced, heavier hairs were used to see whether an increase in the strength of the stimulus served to increase the number of responding points. The results of the examination for touch perception are therefore expressed in two parameters on the sensory charts; the number of touch points per square centimeter are indicated by the numerals within the inked squares and the strength of the stimulus, in grams per square millimeter, by the accompanying figures.

The normal thresholds for touch sensation, determined with graduated hairs, range from 0.5 to 2.0 Gm. per square millimeter. Unless otherwise stated on the sensory

2. von Frey, M.: Untersuchungen über die Sinnesfunktion der menschlichen Haut: I. Druckempfindung und Schmerz, Abhandl. d. math.-phys. Cl. d. k. Sächs. Gesellsch. d. Wissensch. **45**:175, 1896.

charts, the threshold for touch sensation on the unaffected side was within this range. The normal number of touch points per square centimeter of skin area ranges from 25 to 35.

Thermal Sensation.—Test tubes containing ice water and very hot water were used in testing thermal appreciation. No effort was made to test for individual hot or cold points in the skin. Therefore the results are expressed in terms of general appreciation of temperature over sizable areas. The responses of the patients as they reported them to the examiner are expressed, so far as possible, in their own words. For example, the notations on the sensory chart "ice-cool" and "hot-warm" mean that tubes containing ice water and hot water applied to an area were felt as cool and warm, respectively. It was impossible to map out the exact limits of the alterations in thermal appreciation, so that the notations apply to the patient's appreciation within the approximate limits of an entire conventional trigeminal division.

Other Modalities.—The results of testing for two point discrimination are charted separately in the cases in which the test was performed. The values are given in the usual fashion, that is, the distance in centimeters between the limbs of the compass at which the two points are first recognized as two distinct stimuli. This test serves as a confirmation of the loss of touch points, as determined in this paper, which should not be confused with the loss of judgment following cortical lesions. Localization of touch sense and the presence of deep pressure sensation are recorded in the protocols whenever they were tested for. A small tubular spring graduated in grams was used to test the deep pressure sense. The sensory alterations of the tongue and oral mucous membranes are also stated in the protocols.

CASE PROTOCOLS

CASE 1.—E. v. B. had had a previous injection of alcohol into the second division of the trigeminal nerve for relief of neuralgia. Prior to tractotomy there were slight residual hypalgesia and hypesthesia in this division.

Five days after tractotomy there was analgesia to 40 Gm. pressure or more in all three divisions. This analgesia extended slightly down the anterior surface of the neck. The threshold of touch perception was elevated to between 5 and 6 Gm. in the first division and to between 4 and 5 Gm. in the second and third divisions. The number of touch points per square centimeter was not measured. Temperature sensation was moderately blunted in the first division, and both ice water and hot water were experienced as mildly warm in the second and third divisions.

Eleven months after operation the analgesia was still complete in all three divisions. There was a marked decrease in the number of touch points per square centimeter, which could not be greatly increased by increasing the strength of the stimulus. For instance, with a 20 Gm. hair only 14 touch points per square centimeter could be located in the first division and with a 6 Gm. hair only 16 points per square centimeter in the third division. Temperature perception had improved in the second and third divisions but was absent over most of the first division. There was a small elevation of the threshold to two point discrimination in the second and third divisions but a considerable increase in the first division.

The buccal membranes, lips and gums were analgesic. The patient experienced occasional chilly sensations in the face, but there were no other subjective facial sensations. There was complete relief from pain.

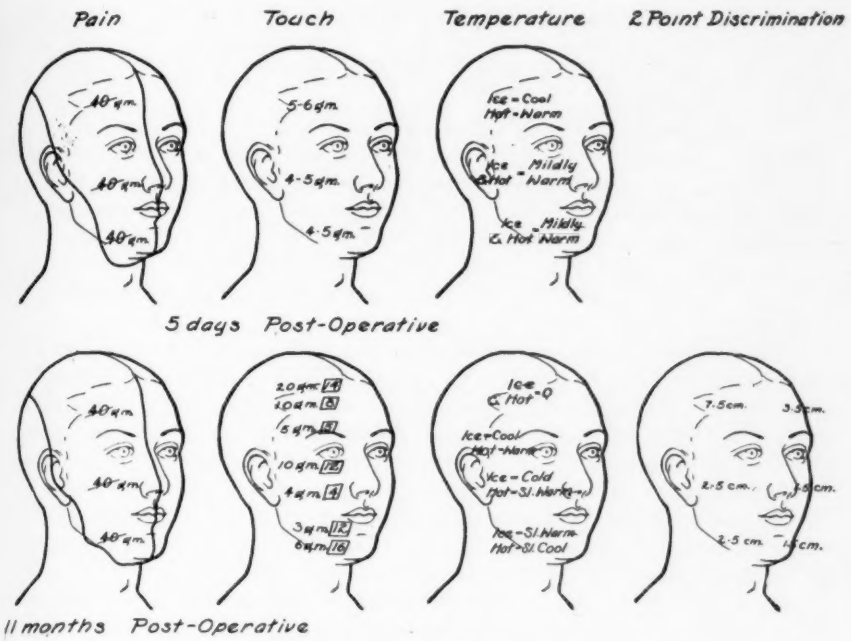

Fig. 2.—Sensory chart in case 1.

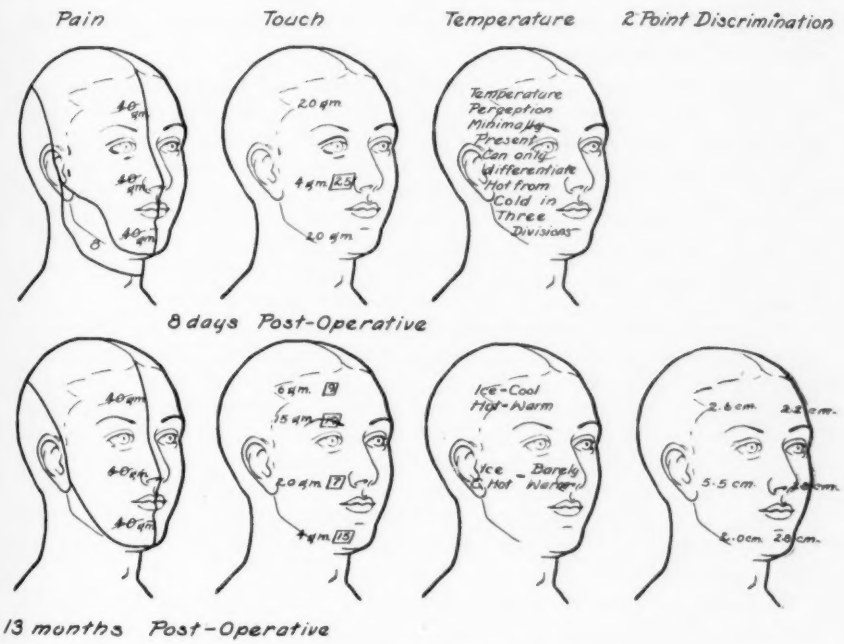

Fig. 3.—Sensory chart in case 2.

CASE 2.—J. E. had previously had an injection of alcohol in the second division of the trigeminal nerve for major neuralgia involving the first and second divisions. Prior to tractotomy there were slight hypalgesia and hypesthesia in the second division.

After tractotomy there was complete analgesia to 40 Gm. thorns in all three divisions. An area on the anterior surface of the neck, as indicated on the sensory chart, had a threshold of 8 Gm. In the first and third divisions 20 Gm. hairs were not perceived, while in the second division, the division into which a previous injection had been made, the threshold to touch sensation was only 4 Gm. and the number of touch points was normal. Temperature perception was minimal in all three divisions, the patient being just able to differentiate hot from cold.

Thirteen months after operation there was still complete analgesia in all three divisions. The hypalgesia over the neck had disappeared. Touch perception in divisions 1 and 3 could now be elicited with 6 and 4 Gm. hairs, and there were 9 and 15 touch points per square centimeter, respectively, in these areas. Whereas the threshold for touch perception had been 4 Gm. in the second division immediately after operation, touch sensation could now be elicited only with 20 Gm. hairs, and the number of touch points per square centimeter was only 7. This is a curious and inexplicable variation. Temperature perception had improved in the first division, but now both hot and cold water were felt as "barely warm" in the second division. Two point discrimination was normal in the first and third divisions but was increased in the second, again possibly as a result of the previous injection of alcohol.

The buccal membranes, lips and gums were analgesic. The patient complained of slight burning sensations about the eye, which, however, were easily tolerated. "Soreness was felt in the eyeball and over the cheek bone. There was complete relief from neuralgic pains.

CASE 3.—W. S. had a tumor of the left antrum, with intractable pain. After tractotomy there was analgesia to 40 Gm. thorns over the first division. This area extended down the side of the nose and around the perioral region. The larger portions of the second and third divisions were sensitive to 30 Gm. thorns. An area over the front of the neck had a threshold to pain perception of 10 Gm. In the first division touch perception was absent until a 20 Gm. hair was used. In the lower two divisions the threshold of touch sense was 4 Gm. The touch points were not counted. Temperature sensation was moderately blunted, ice water being felt as cool and hot water as warm.

Fifteen months after operation the analgesia had disappeared entirely in the second and third divisions, and the threshold to pain sensation was within normal limits (1 Gm.). In the first division there was slight hypalgesia, pain being perceived with 3 or 4 Gm. thorns. Thresholds of touch perception were within normal limits in all three divisions, and the number of touch points per square centimeter was also normal. However, in the first division a moderate reduction in the number of touch points (12 per square centimeter) was noted. Temperature perception was mildly blunted in the first division, and normal in the second and third divisions. Two point discrimination was essentially normal on the side of operation.

The buccal membranes, tongue and gums were fully sensitive to pain sensation. There was complete relief from pain.

CASE 4.—M. T. suffered from major trigeminal neuralgia involving the second division. After tractotomy there was analgesia to a 40 Gm. thorn in all three divisions. An area under the ramus of the jaw and extending on to the neck was markedly hypalgesic to a threshold of 30 Gm., and a small area extending farther down the neck had a threshold of 20 Gm. The threshold for touch perception was 4 Gm. in all three divisions. There was a notable reduction in the number of touch points per square centimeter in the first and second divisions but a normal number in the third division. Temperature sensation was lost in the first division but only slightly blunted in the second and third divisions.

Fourteen months after operation the disturbance of pain sensitivity had entirely disappeared in all three divisions, the threshold being normal (0.5 Gm.). The

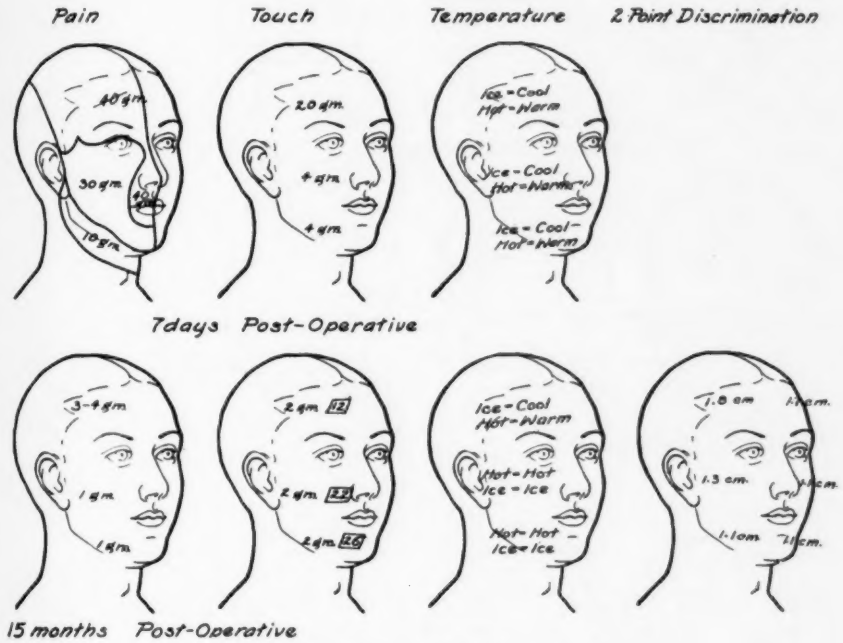

Fig. 4.—Sensory chart in case 3.

threshold for touch perception was also within normal limits (2 Gm.). The number of touch points per square centimeter was also normal. Temperature perception was the same as that on the normal side of the face. Two point discrimination was equal on the two sides of the face. In summary, there was no detectable alteration in sensitivity on either side of the face. The patient did not, however, have any neuralgic pains. She complained only of mild, transitory burning at the angle of the mouth, which did not annoy her much. The lips, tongue and buccal membranes possessed normal sensibility.

Twenty months after operation the patient continued to be free of pain. The objective status of sensitivity in the face was unchanged. Subjectively, there was occasionally a burning sensation around the right eye and the corner of the mouth, which, however, did not bother her.

Case 5.—N. E. had previously had an injection of alcohol in the third division of the right trigeminal nerve for relief of neuralgia. Examination just before tractotomy revealed mild hypalgesia and slight hypesthesia in that division.

After tractotomy there was analgesia in all three divisions. Unfortunately, touch sensation was not tested with graduated hairs, but seemed intact with

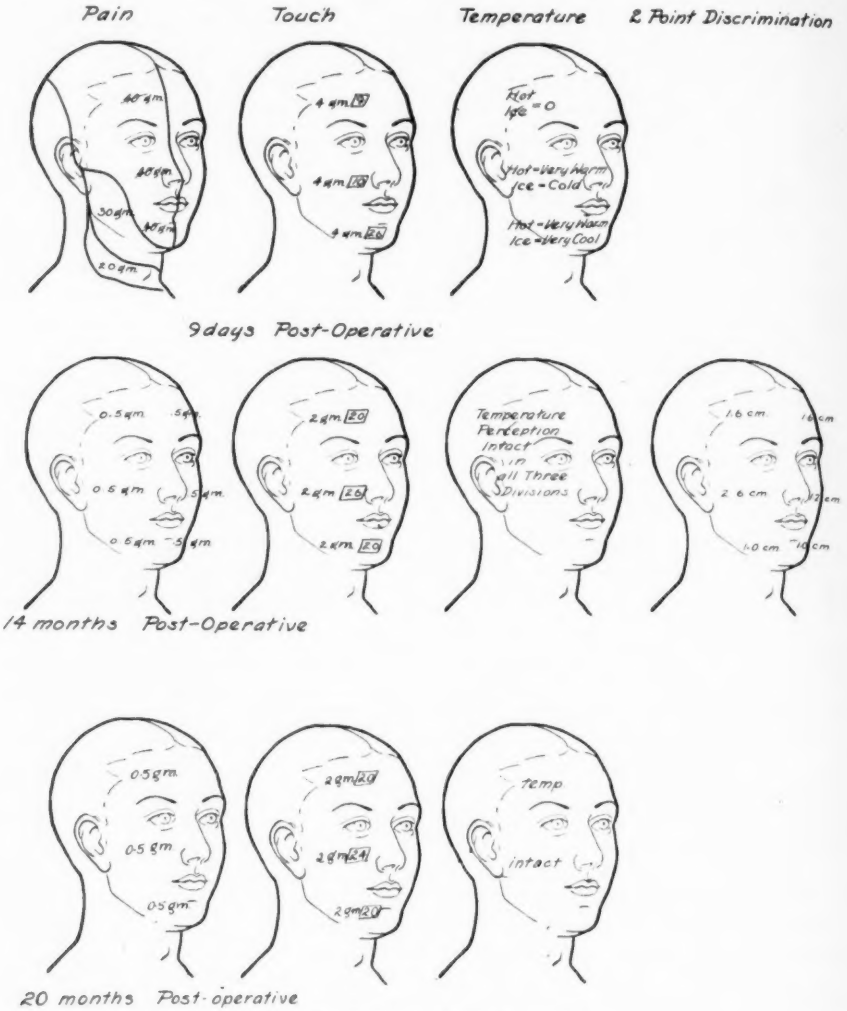

Fig. 5.—Sensory chart in case 4.

ordinary cotton wool testing. There was total thermanesthesia in all three divisions.

Two and one-half months later there was still analgesia in all three divisions of the face except for the vermilion portions of the lips, which were normally sensitive. The tongue, buccal mucous membranes and gums were also sensitive to pain stimulation. The threshold for touch perception was 4 Gm. in division 2,

8 Gm. in division 3 and 5 Gm. in division 1. In division 1 the number of touch points could not be increased by increasing the strength of the hairs to 20 Gm. The touch points in all divisions were greatly decreased in number, being 8, 16 and 12 points per square centimeter in the first, second and third divisions,

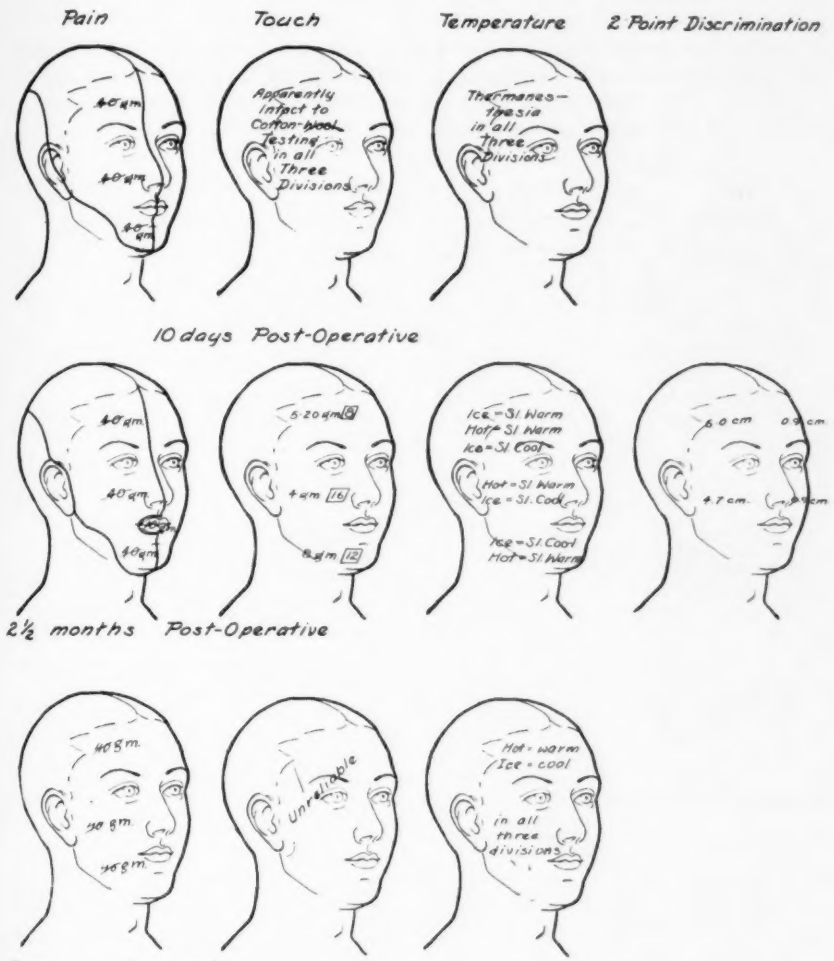

Fig. 6.—Sensory chart in case 5.

respectively. In the first division both ice-cold and hot tubes were felt as slightly warm.

Two point discrimination was greatly impaired in the first and second divisions. Deep pressure sensation was equal on the two sides of the face. Localization of touch sense was precise. There was complete relief from neuralgia.

Nine months after operation the patient continued to be free of pain. The right side of the face was completely analgesic. The data on touch sensation varied too widely to be considered reliable, but there was no numbness of the face.

Case 6.—J. S. had major trigeminal neuralgia involving the first and second divisions of the nerve on the left side, for which alcohol had been injected in the second division. Previous avulsion of the supraorbital nerve had been performed, with failure to remove the nasal branch. Prior to tractotomy analgesia and anesthesia were present in the territory of the supraorbital nerve, with sparing of the nasal branch. There were slight hypalgesia and hypesthesia of the second division.

After tractotomy there was complete analgesia in all three divisions, with an area extending down the upper surface of the neck which had a threshold of 20 Gm. The threshold to touch sensation in the third division was raised to 3 Gm. and that in the second division to 10 Gm. The latter figure is probably

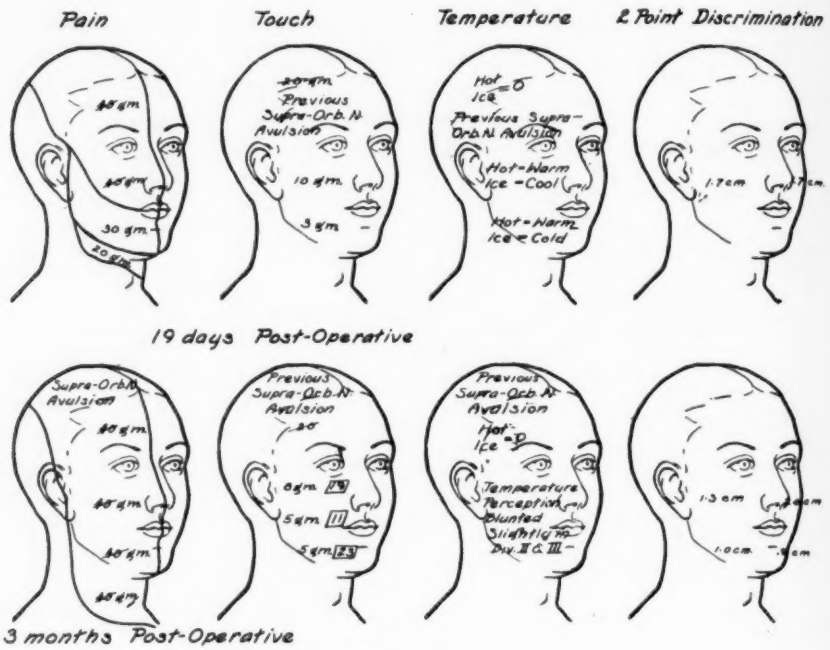

Fig. 7.—Sensory chart in case 6.

accounted for by the previous alcoholic injection. The number of touch points per square centimeter was not determined. There was mild impairment of temperature perception in the second and third divisions. Two point discrimination and deep pressure sensation were equal on the two sides of the face.

Three months after operation analgesia was still present in all three divisions and extended down the front of the neck almost to the clavicle. This loss in pain perception was greater and more extensive than that noted at examination immediately after operation. The disparity was possibly due to the original lack of cooperataion of the patient. The threshold to touch perception was 5 Gm. in the third division, although with 3 Gm. hairs occasional touch sensations were experienced. With 5 Gm. hairs there were 23 touch points per square centimeter in the third division and 11 touch points per square centimeter in the second division. Temperature sensation was slightly blunted in the second and third divisions. Two point discrimination, deep pressure sensation and tactile localiza-

tion were normal on the side of operation. The buccal mucous membranes, tongue and gums were insensitive to pain stimulation.

There was complete relief from trigeminal neuralgia. The patient complained of a feeling of "soreness" around his eye and cheek and a slight burning and tingling sensation at the angle of his nose, which disappeared on rubbing.

CASE 7.—R. A. suffered from symptomatic trigeminal neuralgia involving the second division on the left side, engrafted on multiple sclerosis. Injection of alcohol in this division had previously been made. Testing before tractotomy revealed a slight loss of sensation in the second division.

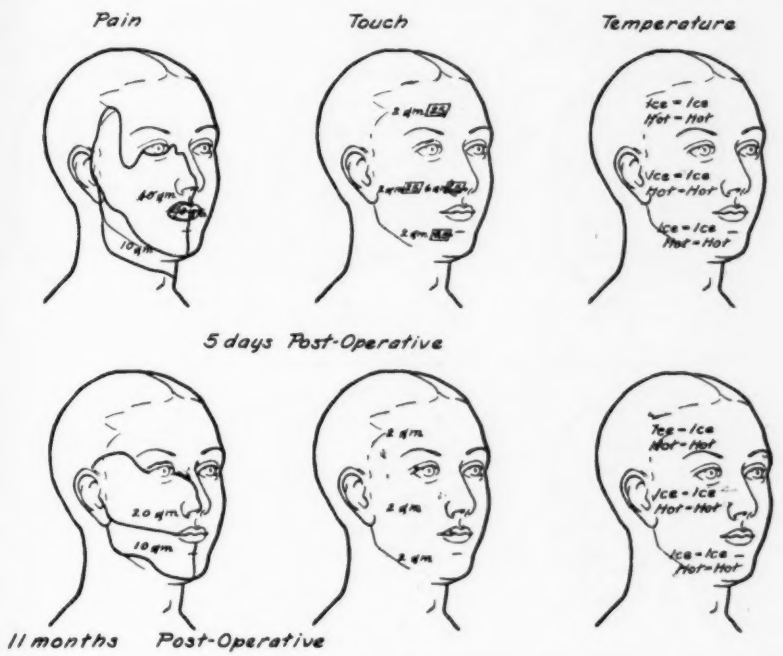

Fig. 8.—Sensory chart in case 7.

After tractotomy there was analgesia in the second and third divisions, but the upper and lower lips were sensitive to 10 Gm. thorns. The tongue was also sensitive. An area with a threshold of 10 Gm. extended a short distance down the neck. There was a normal complement of touch points in all three divisions, and the threshold was 2 Gm. in all divisions except for a small area on the upper lip and nose, which had a threshold of 6 Gm. Temperature sensation was intact in all three divisions of the face.

Eleven months after tractotomy the analgesia had largely faded. In the second division there was pain sensitivity to 20 Gm. thorns and in the third to 10 Gm. thorns. The entire left side of the face was sensitive to 2 Gm. hairs. Temperature sensation was normal. The buccal mucosa, lips and tongue were normally sensitive.

At the time the patient was examined there had been a return of severe neuralgia involving the second division for three months, and it became necessary to section the sensory root for relief of pain. In addition, the patient complained of mild, but annoying, sensory disturbances in his face, consisting of prickling and "pins and needles" sensations, for which he rubbed his face with liniment. He also had the sensation of ants walking on his face and the illusion that his nose was watering.

Case 8.—H. W. had carcinoma of the left antrum, with intractable pain in the second division of the trigeminal nerve. After tractotomy there was complete analgesia in all three divisions of the face. In an area on the upper portion of

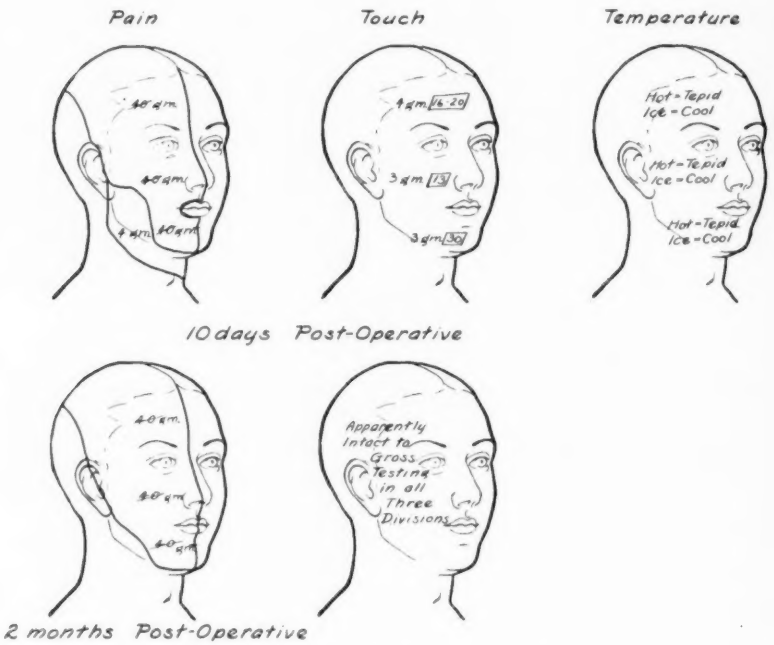

Fig. 9.—Sensory chart in case 8.

the neck the threshold was 4 Gm. The threshold to touch sensation was slightly raised, being 4, 3 and 3 Gm. in the first, second and third divisions, respectively. The number of touch points per square centimeter was moderately reduced in the second division, slightly reduced in the first and normal in the third. Temperature sensation was moderately blunted in all three divisions. Deep pressure sensation was equal on the two sides of the face.

Two months after operation there was still complete analgesia in the three divisions. Touch sensation, unfortunately, was not examined with graduated hairs, but with cotton wool it appeared normal.

The patient was entirely relieved of pain for the duration of her life. It was possible to treat her intensively with roentgen rays and to perform operations on the tumor without the use of anesthesia.

CASE 9.—H. H. had carcinoma of the right mandible, with severe intractable pain. After tractotomy there was complete analgesia in all three divisions of the face. An area just responsive to a 40 Gm. thorn extended down on the neck. The threshold to touch sensation was 4 Gm. in the first division, the number of touch points being reduced to 10 per square centimeter. The number of points could not be increased by using an 8 Gm. hair. The threshold to touch perception was 4 Gm. in the lower two divisions, but the number of touch points was normal. In the first division both ice and heat were felt as warm, and in the second division ice gave no sensation and heat was experienced only as slightly warm. Thermal sensations were better in the third division.

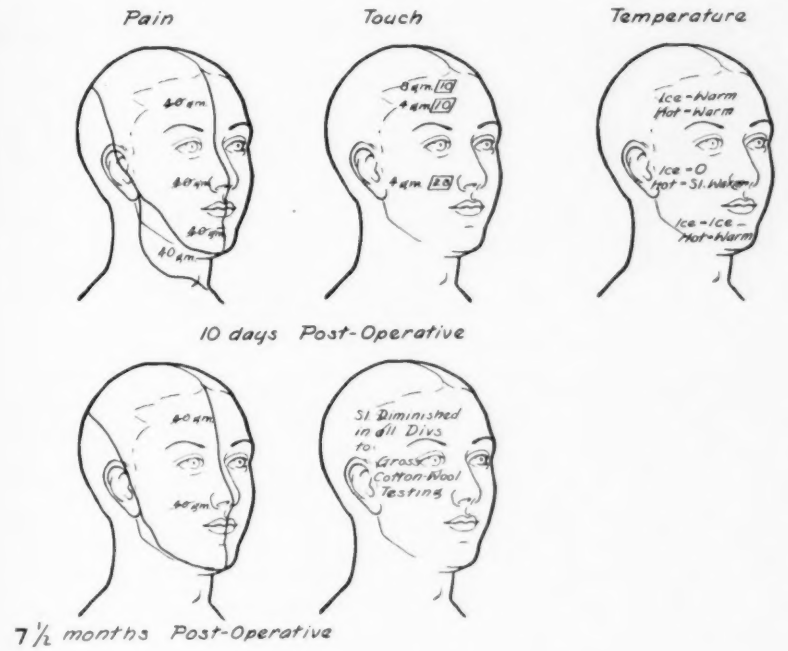

Fig. 10.—Sensory chart in case 9.

There was hemihypalgesia of the left extremities and the left side of the body, the only instance in our experience in which a crossed sensory (Wallenberg) syndrome was produced.

Seven and one-half months later there was still analgesia in all three divisions, so profound that the patient subsequently tolerated, in another hospital, surgical resection of the mandible without anesthesia. At examination in this hospital, in which graduated hairs were not used, ordinary cotton wool testing revealed slight but definite hypesthesia in all three divisions.

CASE 10.—A. W. suffered from major neuralgia involving the third division of the trigeminal nerve, for which an injection of alcohol was made two weeks before operation. Testing before operation showed normal sensitivity to thorns and hairs except for a small area below the left side of the lower lip, in which

there were residual hypalgesia and hypesthesia. In this area only thorns of 8 Gm. or more were felt and touch sense was absent for 20 Gm. hairs.

Temperature sensibility was entirely normal except in this small area, where it was slightly reduced. Two point discrimination was equal on the two sides of the face.

Eleven days after tractotomy there was complete analgesia to 40 Gm. thorns in all three divisions of the nerve. In the first division the threshold to touch sensation was 3 Gm., but only 2 points per square centimeter were responsive. With 4 Gm. hairs there were 6 points and with 8 Gm. hairs 14 points. Testing with 20 Gm. hairs showed all points (25 sq. cm.) to be responsive. In the second and third divisions the threshold was also 3 Gm., but the number

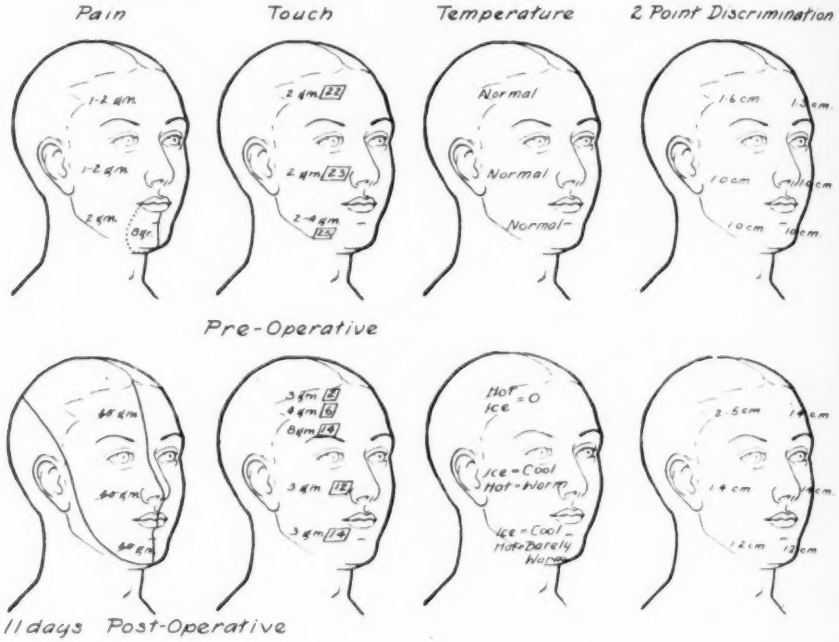

Fig. 11.—Sensory chart in case 10.

of touch points was approximately half the normal. Tubes containing both ice and hot water gave no sensation of temperature in the first division. In the second and third divisions perception of both thermal modalities was present, though notably blunted. Two point discrimination was equal in the second and third divisions, but in the first division the interval between the compass points before they were recognized as two points was almost twice that on the normal side.

The left half of the tongue and the mucous membrane of the lower lip and the floor of the mouth were analgesic, but the sensitivity of the buccal membranes of the cheek, the upper gum and lip and the hard palate was equal to that of the normal side. There was complete relief of pain.

Case 11.—E. P. had melanosarcoma of the left eye and orbit, with intractable pain in the face. After tractotomy there was analgesia in all three trigeminal

divisions. An area responding to 8 Gm. thorns extended down on the neck; below this area was a strip in which the threshold was 2 Gm. With 4 Gm. hairs there were only 4 touch points per square centimeter in the first division. With 4 Gm. hairs there were 16 points in the second division and 35 points in the third division. Both ice-cold and hot tubes were felt as warm in all three divisions. Deep pressure sensation was equal on the two sides of the face. Localization of touch sense was equal on the two sides. There was complete relief of pain after operation. Six months later the patient again complained of pain in the head, which was probably due to extension of the tumor outside the limits of the trigeminal nerve.

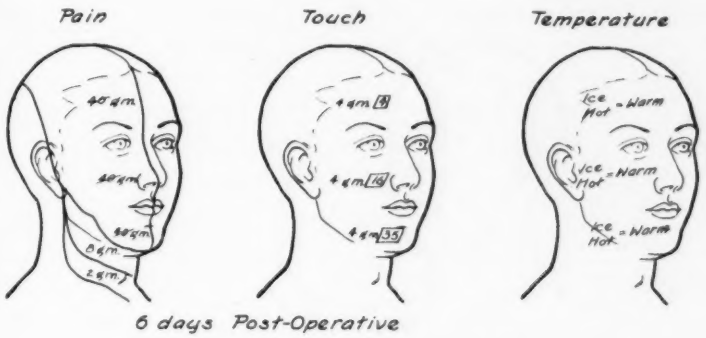

Fig. 12.—Sensory chart in case 11.

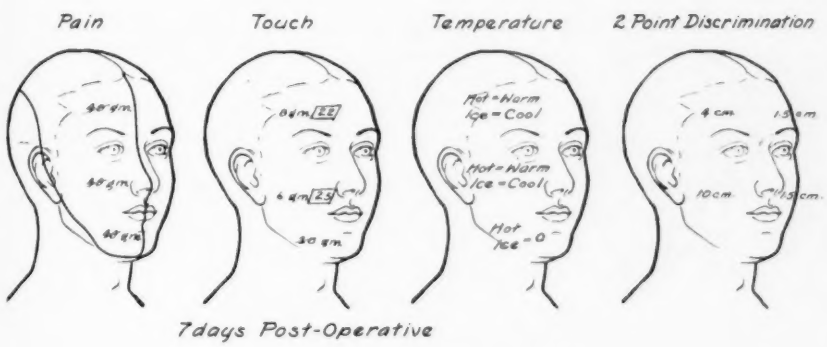

Fig. 13.—Sensory chart in case 12.

CASE 12.—A. P. had a malignant tumor of the left parotid gland. After tractotomy there was analgesia to 40 Gm. thorns in all three trigeminal divisions. The threshold to touch sensation was 8 Gm. in the first division, with 22 touch points per square centimeter. In the second division there was a threshold of 6 Gm., with 25 points per square centimeter. In the third division touch sensation was not present to 20 Gm. hairs, indicating anesthesia for all practical purposes. In the upper two divisions temperature sensation was present, though moderately blunted. In the third division ice was not appreciated at all, but hot water was felt as warm. There was a great decrease in two point discrimination, being 4 cm. in

the first division and 10 cm. in the second division, while on the intact side the appreciable interval was only 1.5 cm. Pain was completely relieved for the five months' survival period.

Case 13.—J. K. had carcinoma of the left mandible, with intractable pain. After tractotomy there was analgesia to 40 Gm. thorns in all trigeminal divisions. The number of touch points per square centimeter was normal in all three divisions, but the thresholds to touch sensation were considerably raised, being 10, 6 and 6 Gm. in divisions 1, 2 and 3, respectively. Pain was completely relieved during the six months' survival period.

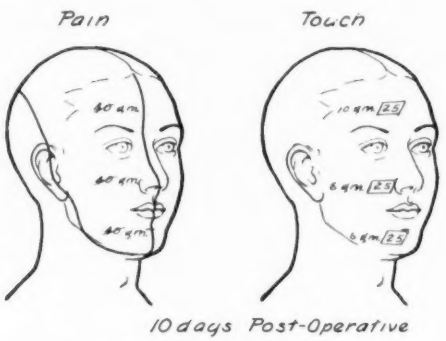

Fig. 14.—Sensory chart in case 13.

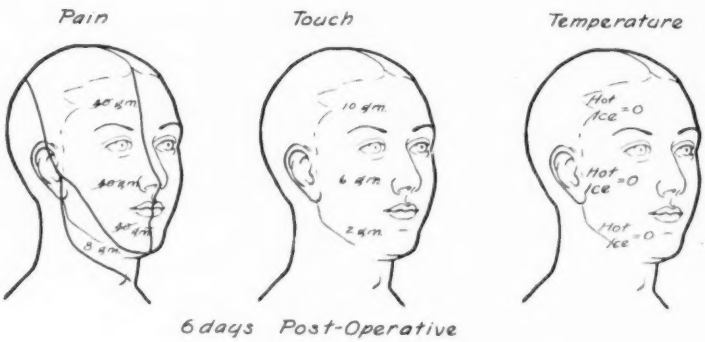

Fig. 15.—Sensory chart in case 14.

Case 14.—A. McL. had carcinoma of the left mandible, with severe intractable pain. After tractotomy there was analgesia to 40 Gm. thorns in all divisions of the nerve. An area with a threshold to pain perception of 8 Gm. extended down the neck. The number of touch points per square centimeter was not studied, but the thresholds to touch sensation were raised. In the first division touch perception was elicited with 10 Gm. hairs and in the second division with 6 Gm. hairs. The threshold was normal in the third division. Thermal perception was entirely absent in all divisions, hot and ice-cold tubes being felt only as touch.

Pain was completely relieved during the seventeen days of postoperative survival.

CASE 15.—C. K. had carcinoma of the tongue, with extension into the floor of the mouth on the right side and severe intractable pain. After tractotomy there was only slight hypalgesia in the lower two divisions of the face. The first division was entirely spared. To gross testing with cotton wool touch sensation appeared to be intact. Thermal sensation was slightly but definitely blunted in all three divisions. Pain was incompletely relieved, though it was much less severe than before operation. This degree of relief was maintained for the month that the patient lived after operation.

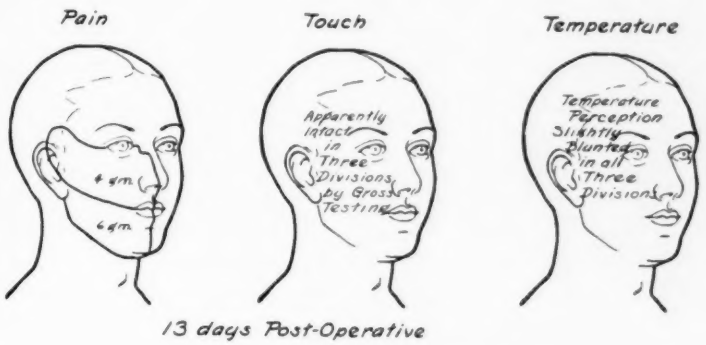

Fig. 16.—Sensory chart in case 15.

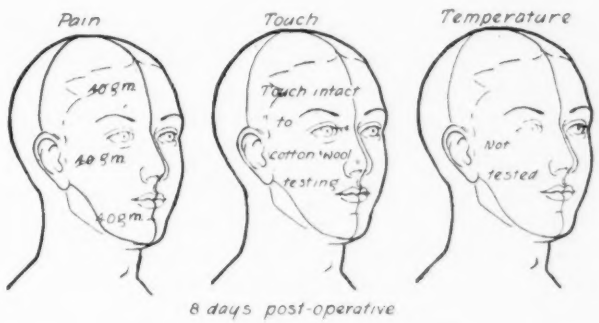

Fig. 17.—Sensory chart in case 16.

CASE 16.—R. J. had carcinoma of the tongue, with extension into the oropharynx and severe intractable pain. After tractotomy there was analgesia to thorns of more than 40 Gm. in all divisions of the trigeminal nerve. Touch sensation was not tested with graduated hairs but appeared normal with cotton wool. Thermal sensation was not tested. There was complete relief of pain in the mouth after operation, but the patient later complained of pain in the top of the head. This was probably due either to extension or to metastases. He survived the operation two and one-half months.

CASE 17.—J. G. had carcinoma of the left antrum and the left side of the maxilla. After tractotomy there was analgesia to 40 Gm. thorns in all trigeminal divisions.

Touch sensation was not tested for, since the patient was operated on before we became interested in the finer disturbances of touch sensibility. Thermal sensation was moderately blunted in all three divisions. The patient was completely relieved of pain for the eight months of his survival.

Case 18.—J. S. had major trigeminal neuralgia involving the right second and third divisions, of two years' duration. Five and one-half weeks after tractotomy there was complete analgesia in all three divisions of the face. The number of touch points per square centimeter was slightly reduced in all three divisions, but the threshold was considerably raised in the second and third divisions, 8 Gm. hairs

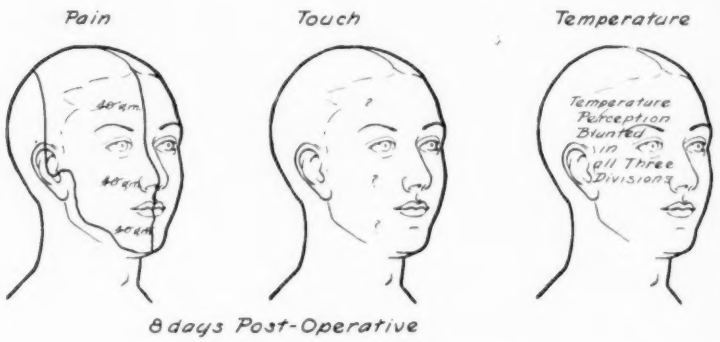

Fig. 18.—Sensory chart in case 17.

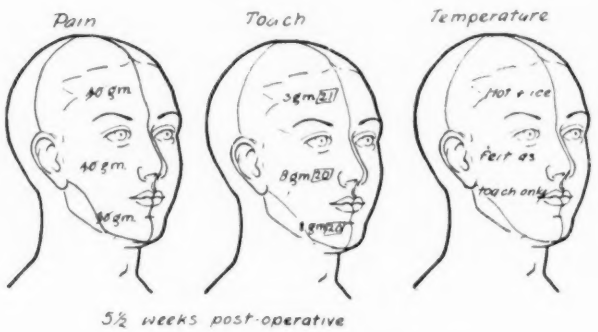

Fig. 19.—Sensory chart in case 18.

being required to elicit touch perception. In the first division, however, 3 Gm. hairs were felt. Tubes containing both hot water and ice water were experienced only as touch. Five weeks after operation the patient was entirely free of neuralgic pains, but she continued to experience a sensation described as between itching and burning over the greater portion of the face on the side of operation. This was not particularly disagreeable and had been present between her neuralgic attacks before operation.

PHYSIOLOGIC AND ANATOMIC COMMENT

There are still a number of unsolved problems concerned with the distribution, course and function of the fibers contained within the

descending tract of the trigeminal nerve. The present communication, which deals exclusively with sensory studies following surgical transection of the descending tract, can contribute, of course, to only a few of them.

Touch Sensation.—The older view, derived from clinicopathologic observations, was that the descending tract is composed exclusively of fibers conducting pain and thermal sensations. Fibers mediating touch sensation, after entry into the brain stem, supposedly go directly to the main sensory nucleus of the trigeminus nerve. This dissociation was held to explain the clinical observation that after thrombosis of the posterior inferior cerebellar artery touch sensation was unaffected while the involved side of the face was analgesic and thermanesthetic.[3] This opinion was held so firmly that Stopford,[4] in a review of the literature on thrombosis of the posterior inferior cerebellar artery, declared that in 2 cases in which authors reported some loss of tactile sensibility the lesion must necessarily have extended into the main sensory nucleus of the trigeminus. Gerard,[5] reviewing 39 cases from the literature, came to the same conclusion. However, as Walker[6] recently pointed out, touch sensation in these cases was tested with cotton wool. This relatively crude method is unsatisfactory when seeking for finer alterations. Walker made tests with graduated von Frey hairs in 2 cases of thrombosis of the posterior inferior cerebellar artery and demonstrated a slight but unequivocal diminution in tactile sensibility on the involved side of the face. Though his technic of testing is open to certain theoretic objections, his point seems to be clearly proved. Furthermore, in performing tests in 2 cases after intramedullary tractotomy, he was able to demonstrate diminution in touch sensitivity, as did Grant, Groff and Lewy[1] in 10 cases. The fact that Sjöqvist[7] insisted that touch sensation after tractotomy is unaffected may be ascribed to his use of cotton wool as the test stimulus. However, Smyth,[8] reporting a case of tractotomy in which operation was performed by Jackson, insisted that touch sensation was entirely intact as tested with von Frey hairs.

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3. Spiller, W. G.: Remarks on the Central Representation of Sensation, J. Nerv. & Ment. Dis. **42**:399, 1915.

4. Stopford, J. S.: The Function of the Spinal Nucleus of the Trigeminal Nerve, J. Anat. **59**:120, 1924.

5. Gerard, M. W.: Afferent Impulses of the Trigeminal Nerve, Intramedullary Course of Painful, Thermal and Tactile Impulses, Arch. Neurol. & Psychiat. **9**: 306 (March) 1923.

6. Walker, E. A.: Anatomy, Physiology and Surgical Considerations of the Spinal Tract of the Trigeminal Nerve, J. Neurophysiol. **2**:234, 1939.

7. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve, Acta psychiat. et neurol., 1938, supp. 17.

8. Smyth, G. E.: The Systemization and Central Connections of the Trigeminal Nerve, Brain **62**:41, 1939.

Our own studies in 18 cases following tractotomy shed some light on the differences between the assertions of Walker and of Smyth. The clue to the situation depends on the method of testing for touch sensation with graduated hairs. If an area of skin 1 sq. cm. is systematically explored with the lightest perceivable stimulus, as described in the section on method, quantitative abnormalities of touch sensation may evidence themselves in several ways. The number of touch points found may be reduced while the threshold for those present may be normal, a condition termed penesthesia by Lewy.[9] The number of touch points may be normal though the threshold of stimulus may be raised in all of them, a condition customarily termed hypesthesia. Last, the number of touch points may be reduced while the remaining ones have an elevated threshold, a condition termed penesthesia plus hypesthesia. Thus, alterations in touch sensitivity must be reckoned with regard to two closely related but different vectors. For instance, in case 10 the threshold was not higher than 3 Gm. per square millimeter, but the number of responsive touch points was notably reduced, in one area to 2 per square centimeter. On the other hand, in cases 3, 8, 9, 12, 13, 14 and 18 the threshold was raised to varying degrees but the number of touch points per square centimeter was only slightly reduced. In cases 1 and 2 a pronounced degree of both penesthesia and hypesthesia was found, while in cases 4, 5, 6 and 11 there were only a slight decrease in the number of touch points and a slight increase in threshold. In case 7 tactile sensibility was almost entirely normal, but the incision was inadequate, as indicated by the later fading of the sensory loss and the return of neuralgia. In 14 of the 15 cases studied with graduated hairs there was definite impairment in tactile sensibility. We therefore agree with Walker's observation. Although Smyth did not specifically state his method of testing, we are inclined to believe that he did not investigate the number of touch points per square centimeter but assumed that a normal threshold represented an intact appreciation of touch sensation.

The varying degrees of penesthesia and hypesthesia observed are probably explainable by small differences in the length and depth of the medullary incision and by individual variations in the composition of the descending tract. The latter factor must be considerable, since the loss of touch sensation was rather noticeable in some instances. In fact, in case 2 the patient complained of a feeling of numbness over his forehead. This observation, not heretofore reported in experiences with tractotomy, emphasizes the wide variability in the number of fibers conducting tactile sensation in the descending trigeminal tract. Inspec-

9. Lewy, F. H.: The Role of Cervical Nerves in Facial Sensation and the Quantitative Disturbance of Sensitivity in Major Trigeminal Neuralgia, Am. J. M. Sc. **196**:509, 1938.

tion of the sensory charts also shows how the alterations in touch sensation may vary from one division to another in the same subject.

The anatomic basis for the fact that touch sensation is apparently represented in the descending tract may be found in fiber analyses carried out on man [7] and animals.[5] While investigators have reported a great predominance of small fibers, of less than 4 microns in diameter, in the descending tract, they have also seen small but varying numbers of large fibers, of more than 4.8 microns in diameter. According to present views, the small fibers conduct pain impulses and the large fibers touch impulses. There are, therefore, in these analyses a suggestion of the presence of touch fibers in the descending tract and therefore an explanation of the clinical findings reported by Walker and ourselves.

Cutaneous Sensitivity Versus Sensitivity of the Mucous Membranes.—When a peripheral division of the trigeminal nerve is severed or when the sensory root is transected, not only the cutaneous territories but the corresponding mucous membranes are made analgesic. It has been recognized for some time that the fibers mediating painful sensations from the labial and lingual membranes and those from the cutaneous areas pursue different paths within the descending tract.[10] Anatomists [11] have localized the fascicles conveying pain sensation from the labial and lingual membranes in the most dorsomedial portion of the descending tract. Almost no information can be found in the literature regarding the distribution of the pain fibers from the buccal, gingival and palatal mucous membranes. The sensory state of these membranes has, unfortunately, more often than not been neglected in the clinical studies of thrombosis of the posterior inferior cerebellar artery. With a relatively massive lesion, such as that produced by a thrombosed artery, disparities in loss of pain sensation between the skin and the mucous membranes have been occasionally observed. Perhaps the best instance is the report by Cadwalader.[12] In his case there was an area on the cheek only the size of a half-dollar in which pain and temperature sensations were disturbed, but the mucous membranes lining the cheek, pharynx, gingivae and fauces were almost analgesic. On the other hand, analgesia of the skin has been associated with intact sensitivity of the mucous membranes.[13]

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10. Wallenberg, A.: Anatomischer Befund in einem als Blutung in die rechte Brückenhälfte usw. aus dem Ram. central. arter. radicular N. facialis dextrius geschilderten Fälle, Deutsche Ztschr. f. Nervenh. **27**:436, 1904.

11. Winkler, C.: De bouw van het zenuwsteelsel **2**:26, 1920.

12. Cadwalader, W. B.: Thrombosis of the Right Posterior Inferior Cerebellar Artery Causing Bilateral Paralysis of Muscles of Deglutition, J. Nerv. & Ment. Dis. **41**:375, 1914.

13. Müller, E.: Ueber ein eigenartiges scheinbar typisches Symptomenbild bei apoplectiformer Bulbarlähmung, Deutsche Ztschr. f. Nervenh. **31**:452, 1906.

Our experiences with tractotomy have demonstrated the most bizarre forms of dissociated analgesias of the skin and mucous membranes, which make it seem probable that the fibers conducting pain sensation from the entire oral mucous membranes possess special pathways within the trigeminal tract. In case 10, for example, the mucous membrane lining the cheek and that of the upper gum, upper lip and palate were normally sensitive, while the tongue and the mucous membrane lining the lower lip were analgesic. Yet all three cutaneous areas of the trigeminal distribution were equally analgesic. In cases 3, 4, 5 and 7 the mucous membranes of the cheek, tongue and lip were spared, though the corresponding cutaneous areas were analgesic. In cases 1, 2 and 6 the analgesia of the mucous membranes corresponded to that of the skin. We are inclined to think, on the basis of our operative results, that the pain fibers from the oral mucous membranes lie most medial in the tract. This would fit in with the fairly well agreed-on site of the pain fibers from the lips and tongue, which, as mentioned before, appear to lie most dorsal and medial in the tract.

Pain Versus Thermal Sensibility.—In a number of our cases postoperative sensory examination showed considerable discrepancy in the degree to which pain and temperature were affected. This is not an unexpected observation, for Spiller [3] long ago emphasized this dissociation, which he noted in a case of thrombosis of the posterior inferior cerebellar artery. He concluded that there must be separate pathways for pain and for thermal sensations in the trigeminal tract. His observations have since been verified in numerous case reports of thrombosis of this artery, as well as in the sensory studies following anterolateral chordotomy. Spiller also expressed the idea that heat and cold might conceivably have separate fiber representation. Judging from such a case as the one reported by Breuer and Marburg,[14] in which the only sensory defect, following a thrombotic softening in the descending tract, was loss of cold perception on one side of the face, hot and pain sensations being well perceived, such a dichotomy of thermal sensation appears to exist. Of those who have published accounts of the sensory alterations following tractotomy, only Grant, Groff and Lewy [1] made reference to the dissociation between the loss of thermal and that of pain sensibility. In cases 3, 14, 15 and 18 there was good correspondence between the loss of pain and that of thermal sensibility. Conversely, in cases 4, 6, 7, 8 and 11 there was a notable difference in the degree of loss of the two modalities. In cases 1, 2, 5, 9, 10, 12 and 17 there was a fair correspondence between the two. The differences varied with the divisions of the nerve in the same subject, so that temperature sensation might be entirely lost in one division and fairly well preserved in another.

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14. Breuer, R., and Marburg, O.: Zur Klinik und Pathologie der apoplectiformen Bulbärparalyse, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **9**:181, 1902.

Distribution of the Trigeminal Nerve.—In a number of the sensory charts it will be noted that the area of analgesia extended variable distances down the neck. This was most pronounced in cases 4, 6 and 11. These extensions outline the area of trigeminal innervation which overlaps the upper cervical dermatomes. The representation of the trigeminal nerve in the upper portion of the neck apparently varies widely among persons. The sensory supply of the cervicotrigeminal junction has been previously studied by Lewy,[9] using the method of sensory chronaxia, and our observations merely confirm his original conclusions.

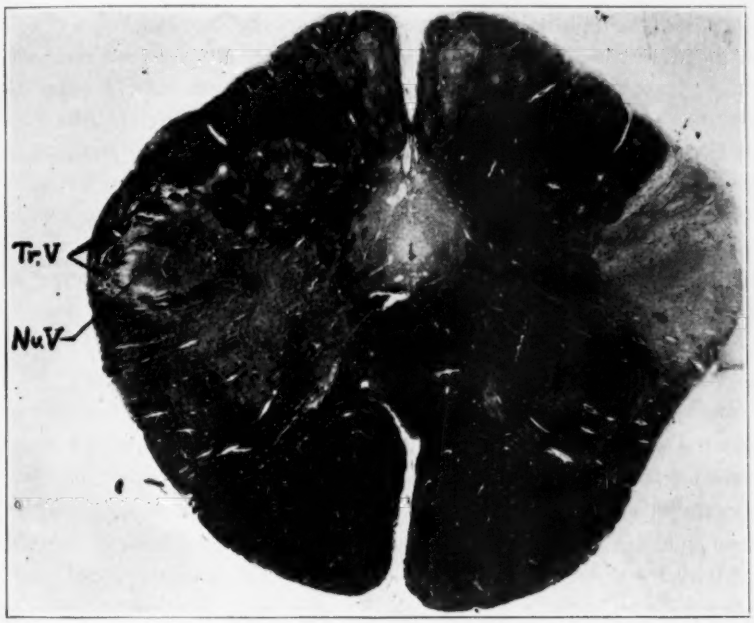

Fig. 20 (case 9).—Cross section of the medulla through the site of the medullary incision, showing that the transection of the descending trigeminal tract was made at the level of the upper part of the pyramidal decussation. The area of surgical destruction on the right side encompasses both the descending tract and the spinal nucleus of the trigeminal nerve. These structures on the left side are appropriately labeled: *Tr. V.*, descending tract; *Nu. V.*, spinal nucleus of the trigeminal nerve. Death occurred eight and a half months after operation.

Though disproved by clinicoanatomic studies, the conception still exists, judging from statements in current textbooks, that lesions of the descending trigeminal tract produce concentric zones of analgesia in the face. In a case of gradually ascending syringobulbia the nose and perioral region are supposed to be first affected, subsequently the middle and lastly the outer zone of the face. This opinion was based on the

belief that the fibers from the central facial zone terminated lowest in the trigeminal tract and those from the middle and outer zones ended in the spinal trigeminal nucleus at successively higher levels. However, it is now generally agreed that the distribution in the descending tract is in terms of peripheral divisions. This is again borne out by our cases 3, 6, 7 and 15, in which the distribution of the analgesia was in terms of peripheral divisions.

Nevertheless, even recent authors have stated that the fibers from the three trigeminal divisions terminate at greatly different levels in the spinal nucleus of the nerve. Thus, Smyth [8] concluded from his studies of thrombosis of the posterior inferior cerebellar artery and of syringobulbia that the ophthalmic fibers descend to the cervical portion of the cord but that the fibers from the maxillary division terminate at the level of the glossopharyngeal nucleus and the mandibular fibers even more rostrad. This conclusion is plainly contradicted by the results in our case 9, in which at the time of the patient's death, eight months after tractotomy, profound analgesia of all three trigeminal divisions existed. Figure 20 shows that the surgical incision was made at the upper level of the pyramidal decussation. At this caudal point in the medulla, 10 mm. below the obex, all three divisions of the trigeminal nerve were still obviously represented in the trigeminal tract.

SURGICAL COMMENT

Aside from the interesting, but academic, considerations which were discussed in preceding paragraphs, this new operation raises for the neurosurgeon and the neurologist problems of practical importance respecting the applicability of tractotomy for the relief of facial pain. These questions, of course, deal largely with the sensory alterations produced by the procedure. Inasmuch as the relief of facial pain is related principally to the production of analgesia, the following discussion will be limited to the modality of pain, and the terms "sensory loss" and/or "sensory defect" will apply only to the reduction in the appreciation of painful stimuli.

Predictability of Sensory Loss.—The certainty of an adequate division of nerve fibers is less in tractotomy than in retrogasserian neurotomy. There are two reasons for this. First, the surgeon cannot see the point of the knife blade when it is inserted into the medulla and so cannot be certain whether the incision is long and deep enough. There is considerable reluctance to incise boldly, since the possibility exists of injuring highly important neighborhood structures. Second, the operation must be performed with the patient under general anesthesia, since the medullary incision is painful and movement must be avoided lest the knife blade be deflected. Therefore, it is impossible repeatedly to test

sensation during the operation, as with chordotomy, to see whether adequate analgesia is being produced, and to cut further if such is not the case. The latter difficulty may be resolved by perfection of technic. Until this is reached, however, it will be impossible to produce a differential analgesia limited to one or two divisions. As a matter of fact, the small size of the descending tract may defeat such efforts even should it be possible to perform the operation with local anesthesia.

Despite these theoretic and practical difficulties, we were able to secure postoperative analgesia involving all three divisions in 15 cases. In 2 cases that are not presented in this study, for reasons stated at the outset, there was no loss of sensation after operation. In another, case 15, only minimal postoperative hypalgesia over the lower two divisions was effected.

Stability of Sensory Loss.—Unfortunately, in only 10 cases could the patient be followed over a considerable period. In 3 cases (3, 4 and 7), as indicated on the sensory charts, there was fading of the sensory loss that was observed immediately after operation. This was most striking in case 4, in which total analgesia in all three divisions completely disappeared over the course of fourteen months, normal sensation being eventually regained. In case 3 analgesia in division 1 and marked hypalgesia in divisions 2 and 3 faded to slight hypalgesia in eleven months.

The gradual disappearance of the sensory defect observed immediately after operation is difficult to explain unless one assumes that operative regional edema may cause more evidence of neural injury than is subsequently apparent. Whatever the reason, a reduction in the extent of the analgesic area can occur in time. Precisely the same diminution in the extent of the analgesia is noted at times after retrogasserian neurotomy. In 6 cases (1, 2, 5, 6, 8 and 9), however, two to eleven months after operation there was still analgesia in all three divisions. In case 18 analgesia is present five and one-half weeks after operation, but the follow-up period has been too short to permit a definite prognosis.

Relief of Pain in Relation to Postoperative Sensory Loss.—In general it has been our experience with tractotomy, as with section of the sensory root of the trigeminal nerve, that the relief of pain is related to the maintenance of the sensory loss. As an example case 7 is cited, in which neuralgia returned in the second division as the analgesia faded. In case 4, in which normal sensation was regained after fourteen months, there was, curiously, no return of the neuralgia. The patient complained only of brief attacks of "burning" at the angle of the mouth. In case 3, in which the analgesia completely disappeared, the antral tumor was success-

fully removed during the period that analgesia was present; so tractotomy served its purpose. In those cases in which late studies showed that the degree of sensory loss was satisfactory there was complete relief of pain.

Sensitivity of the Mucous Membranes.—It was pointed out in a previous paragraph that the mucous membranes may remain sensitive even though analgesia is produced in the skin of the face. Therefore, it is theoretically possible that a painful carcinoma involving the tongue or the oral mucous membranes may go unrelieved even though the cutaneous areas of the trigeminal distribution are rendered analgesic. Again, it is conceivable that a neuralgic "trigger point" could continue to operate and initiate pain, at least in the tongue or gums, even though the skin is rendered analgesic. Only further experience will prove whether these fears are justified; so far this complication has not been encountered. At any rate, it seems desirable that the medullary incision be made deeper, rather than shallower, to avoid the possibility that sensation might not be abolished in the mucous membranes. When the surgical modification that we have described elsewhere is used,[15] slightly increasing the depth of the incision does not apparently damage important structures.

Dysesthesias.—Theoretically, there is no reason that dysesthesias should not follow division of the descending tract. It is well known that thrombosis of the posterior inferior cerebellar artery is frequently followed by severe burning, freezing or lancinating dysesthesia, due apparently to softening in the descending tract. In the 10 cases of tractotomy with late follow-up observations, we have not encountered any severe forms of subjective facial sensation. However, on specific questioning, 5 patients admitted experiencing mild facial sensations of various kinds. Both patients 2 and 6 said that they had a feeling of "soreness" around the eye associated with very slight burning sensations, which were not especially annoying. Patient 1 experienced chilly feelings in the cheek. Patient 7 mentioned mild, though somewhat annoying, prickling sensations, for which he rubbed his face with liniment. He also had the illusion that his nose was watering. Patient 18 had itching and burning sensations, which, however, were also present before operation. For the most part after tractotomy the patient was not aware that there was any loss of sensation in the face except that in shaving or in running the hands over the face, the side of operation felt "a little different from the other." There was no numbness or stiffness of the face, as experienced after section of sensory roots. So far as our material permits a statement, severe, or even very annoying, dysesthesias seem to appear infrequently, if at all, after tractotomy.

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15. Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Complications, Surg., Gynec. & Obst. **72**:747, 1941.

CONCLUSIONS

As a result of the studies in these cases the following conclusions are reached.

1. Touch fibers are present in the descending trigeminal tract.

2. Different pathways for pain sensation from the skin and mucous membranes seem demonstrable within the trigeminal tract. Pain fibers from the oral mucous membranes apparently lie most medially in the tract.

3. Evidence is presented that separate pathways exist for pain and thermal sensibility in the descending trigeminal tract.

4. Further evidence is presented indicating that the distribution of the trigeminal descending tract is in terms of peripheral divisions and that fibers from all three divisions may descend in the tract to a point below the obex.

5. As in cases of subtemporal or subtentorial root section, the stability of sensory loss is not predictable. The area of analgesia may shrink. As this area decreases in size recurrence of pain is possible.

6. Dysesthesias seem more infrequent after tractotomy than after posterior root section by the temporal route.

2839 Ellis Avenue, Chicago.

3400 Spruce Street, Philadelphia.

EFFECT OF CERTAIN CHOLINE DERIVATIVES ON ELECTRICAL ACTIVITY OF THE CORTEX

CHARLES BRENNER, M.D.
AND
H. HOUSTON MERRITT, M.D.
WITH THE TECHNICAL ASSISTANCE OF MARGUERITE G. MAGUIRE, B.A.
BOSTON

The present report deals with the results and interpretation of a series of experiments on the effect of three choline derivatives on the electrical activity of the cerebral cortex of cats. The three compounds tested were acetylcholine chloride, acetylbetamethylcholine chloride (mecholyl chloride) and carbamylcholine chloride (doryl).[1]

METHOD

Adult cats were anesthetized with intraperitoneal injections of dial; both cerebral hemispheres were widely exposed and the dura removed. A total of 57 animals was used. The electrical activity of various cortical areas was recorded with a multichannel Grass electroencephalograph. The stages of amplification in this instrument are condenser coupled, and the recorder writes in ink on a paper tape. This instrument records all frequencies between 2 and 70 per second. Unipolar leads were employed, the stigmatic electrode being formed by a cotton wool wick soaked in physiologic solution of sodium chloride, one end of which rested on the surface of the brain, while the other was wrapped about a chlorided silver wire (fig. 1). The indifferent electrode was formed by two metal buttons fastened with collodion to the animal's ears.

The drugs were dissolved in solutions of physiologic solution of sodium chloride and applied by moistening a small cotton pledget in the solution and laying it on the cortex for a given period. The pledget was then removed, the cortex washed with warm saline solution and the cotton wick electrode applied to the portion of the cortex which had been treated with the drug (fig. 1 *A* and *B*). An alternative technic used in many of the later experiments was to keep the electrode in contact with the cotton pledget itself throughout the period of application of the drug to the cortex (fig. 1 *C*). In this way a continuous record of the electrical activity of the cortex could be obtained during the application of the drug.

This study was aided by a grant from the John and Mary R. Markle Foundation.

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

Read at the Seventy-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 11, 1941.

1. These drugs were furnished by Merck & Co., Inc., Rahway, N. J.

RESULTS

Acetylcholine Chloride.—It was found that the application in this way of solutions of acetylcholine chloride, varying in concentration from 2.5 to 10 per cent, would produce a pronounced localized change in the electrical activity of the cortex, beginning in five to ten minutes after the pledget was applied and reaching a maximum three to ten minutes later. The various types of alteration of electrical activity thus produced are illustrated in figures 2 to 7 inclusive. Changes occurred in both voltage and frequency. The voltage was regularly increased

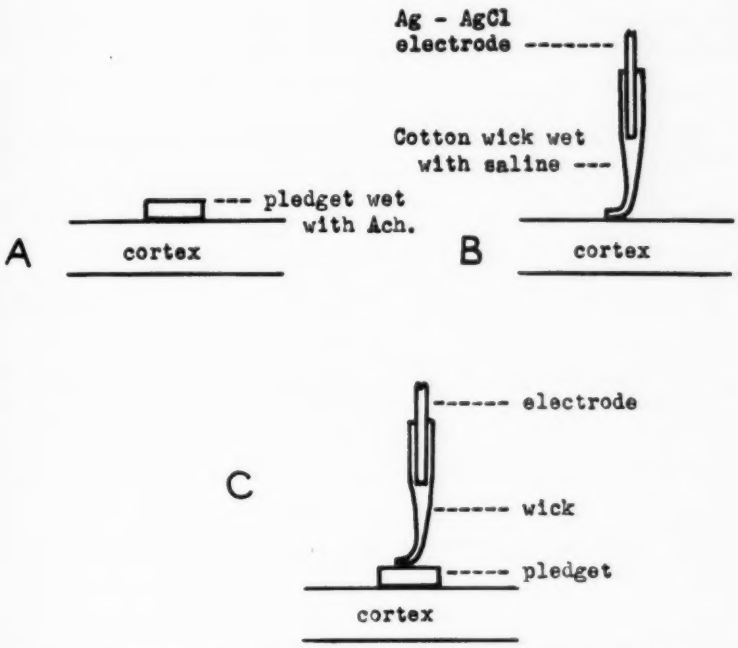

Fig. 1.—Diagrams illustrating technics of applying a solution of acetylcholine chloride and electrodes to the cortex (see text for explanation). In this and in the subsequent figures, *Ach.* means acetylcholine chloride.

to a greater or less extent, while the changes in frequency were more variable. In some responses slow frequencies predominated and in others more rapid ones, the range being from about 4 to 30 per second. All responses showed fluctuations in both frequency and voltage during their course and developed and disappeared progressively rather than abruptly (fig. 3). In some, waves of various frequencies were so combined as to produce a rather irregular record, while others showed more regular wave patterns. It was noted that in any given response the slower frequencies tended to be of higher voltage than the faster

ones. In our experience there was no striking difference in the excitability of various cortical areas, though it seemed in general that the occipital pole was less likely to give fast (i. e., high frequency) waves than other, more anterior regions. We did not attempt application of the drug except to the convexities of the hemispheres.

In the 14 animals to whose cortices we applied acetylcholine alone the electrical response thus produced remained strictly localized to the drugged area and did not spread either to adjacent or to more distant regions. It might be noted here, however, that in 3 of 34 animals the response produced by the application to the cortex of a solution containing both acetylcholine and prostigmine did spread to a symmetric area on the contralateral hemisphere.

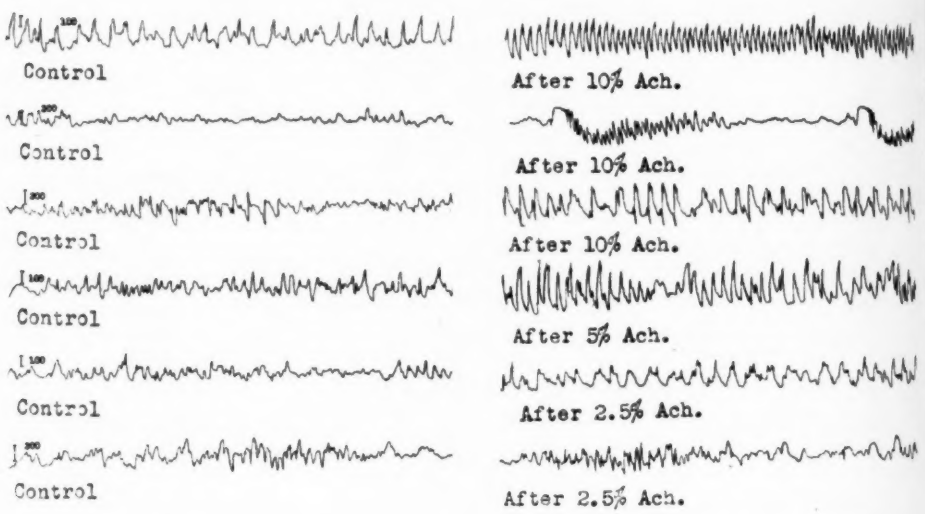

Fig. 2.—Six sample responses to the local application of acetylcholine chloride (*Ach.*). In each case a control record is at the left; the right hand record is from the same cortical area after application of the drug. Each of the twelve samples represents six seconds of record. In this figure and in the following figures signals at the left are expressed in microvolts.

There was, of course, considerable variation from animal to animal in the apparent sensitivity of the cortex to the drug, but in the majority of cases the application of a 10 per cent solution resulted in a pronounced change in the electrical activity of the cortex, a 2.5 per cent solution usually produced a definite though slight response, while with a 5 per cent solution there was a response of intermediate intensity (fig. 2). Solutions of 1.25 per cent strength or less were ineffective.

After removing the acetylcholine and washing the cortex with saline solution the electrical response that had been produced persisted for a few minutes before the record returned to normal. Figure 3 illustrates the gradual development and disappearance of the electrical response to the application of a 5 per cent solution of acetylcholine

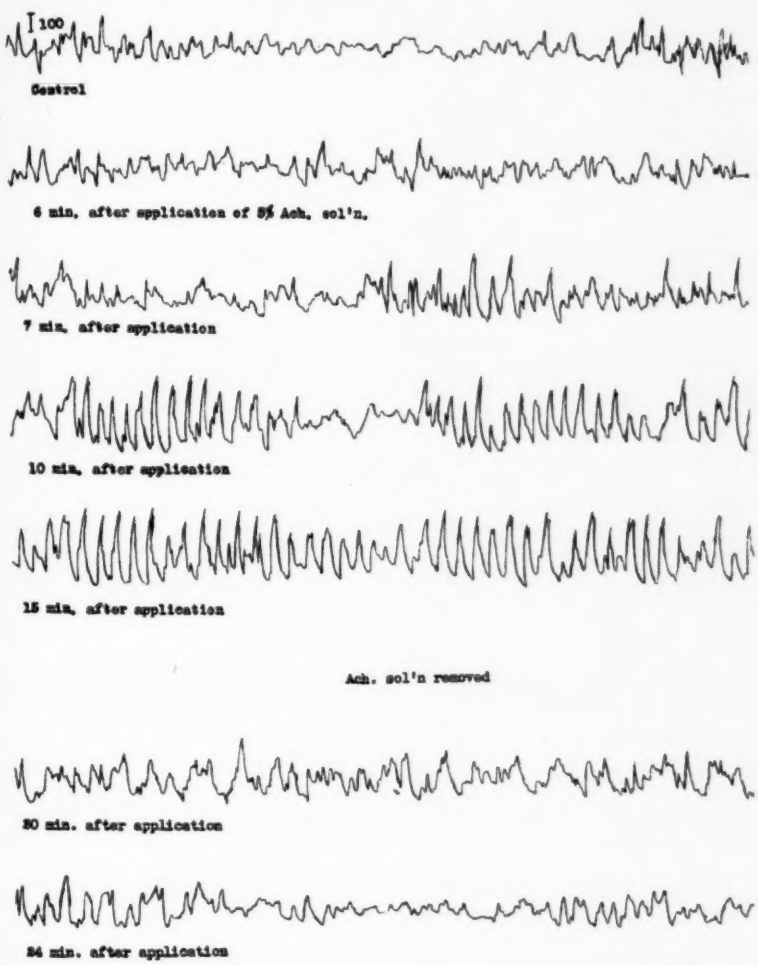

Fig. 3.—Samples from a continuous record of electrical activity before, during and after the application of acetylcholine chloride, illustrating stages in the development and disappearance of the electrical response. Each segment represents six and a half seconds of record.

chloride. We found no great constancy in the duration of the response after the removal of the drug. The period might vary from two to

fifteen minutes. It seemed in general that the more intense the electrical response the longer it was likely to last (table 1).

If, instead of removing the acetylcholine solution from the cortex at the end of ten or fifteen minutes, it was left in contact with the

TABLE 1.—*Relation Between Degree and Duration of Electrical Response to Acetylcholine Chloride*

Degree of response	+ (minimal)	2+	3+	4+ (maximal)
Average duration after removal of acetylcholine, min.	3	5	7	11
Limits of duration, min.	2-3	2-9	6-8	7-15

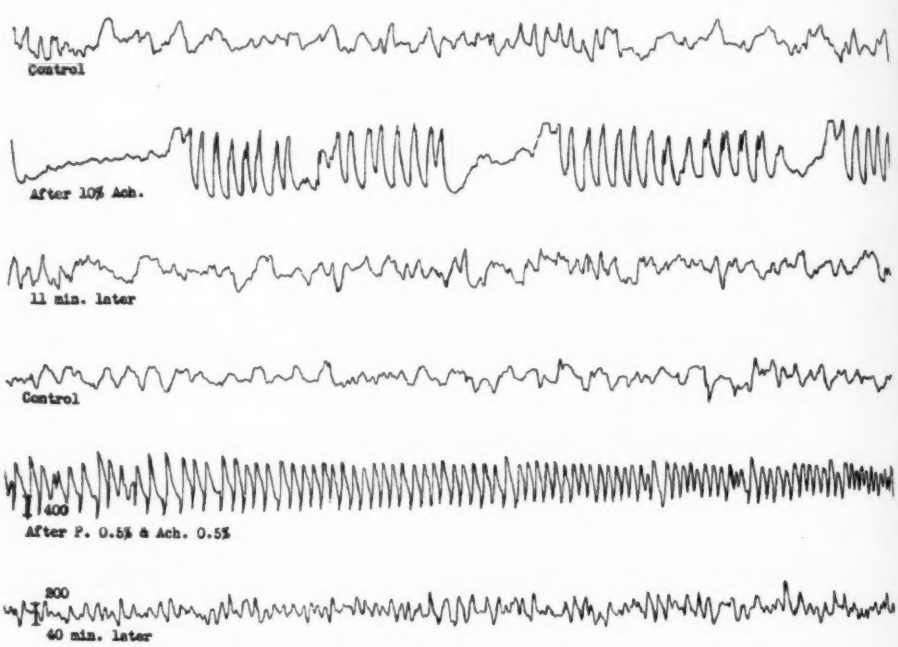

Fig. 4.—Electrical response first to acetylcholine chloride alone and then to a mixture of acetylcholine chloride and prostigmine sulfate, applied successively but each to a different cortical area of the same cat. Each segment represents eight seconds of record. Note that the amplification in the fifth tracing is only half that in the other five.

cortex, the electrical response continued, although the intensity declined somewhat. In 1 experiment the response was thus prolonged for forty minutes, and it is quite likely that it could have been prolonged even longer had we attempted to do so.

Since certain of the physiologic effects of acetylcholine are inhibited by atropine (the "muscarine effect") while others are not ("nicotine effect"), two experiments were designed to test in which of these categories the action of acetylcholine on the cortex should be placed. It was found that intravenous injection of atropine sulfate (in a dose of 1 mg. per kilogram of body weight) neither altered appreciably nor shortened the electrical response to the previous application of acetylcholine chloride and that the application of acetylcholine to the cortex ten to twenty-five minutes after the injection of atropine pro-

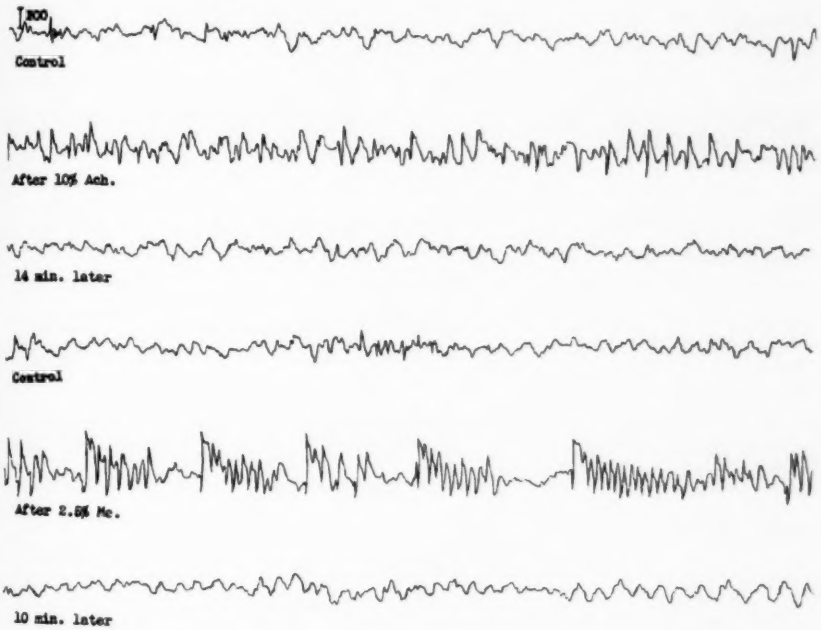

Fig. 5.—Electrical responses first to acetylcholine chloride and then to acetyl-betamethylcholine (mecholyl) chloride. Each segment represents seven seconds of record.

duced an electrical response quite comparable in intensity and duration to that produced in the same animal before atropinization.

It was found that the activity of solutions of acetylcholine chloride was greatly enhanced by the addition of small amounts of prostigmine methylsulfate [2] (fig. 4). Thus, a definite response was generally observed after the application of a 0.08 per cent solution of acetylcholine chloride containing 0.5 per cent of prostigmine methylsulfate,

2. The prostigmine methylsulfate was furnished by Hoffmann-LaRoche, Inc., Nutley, N. J.

while a solution containing 0.5 per cent each of acetylcholine chloride and prostigmine methylsulfate ordinarily produced a striking response. Moreover, under these circumstances, instead of disappearing in a few minutes, the response lasted for forty-five to ninety minutes or even longer (fig. 4).

Acetylbetamethylcholine Chloride (Mecholyl Chloride).—The application of a solution of this compound to the cerebral cortex in the manner previously described produced an electrical response indistinguishable from that produced by acetylcholine chloride (fig. 5).

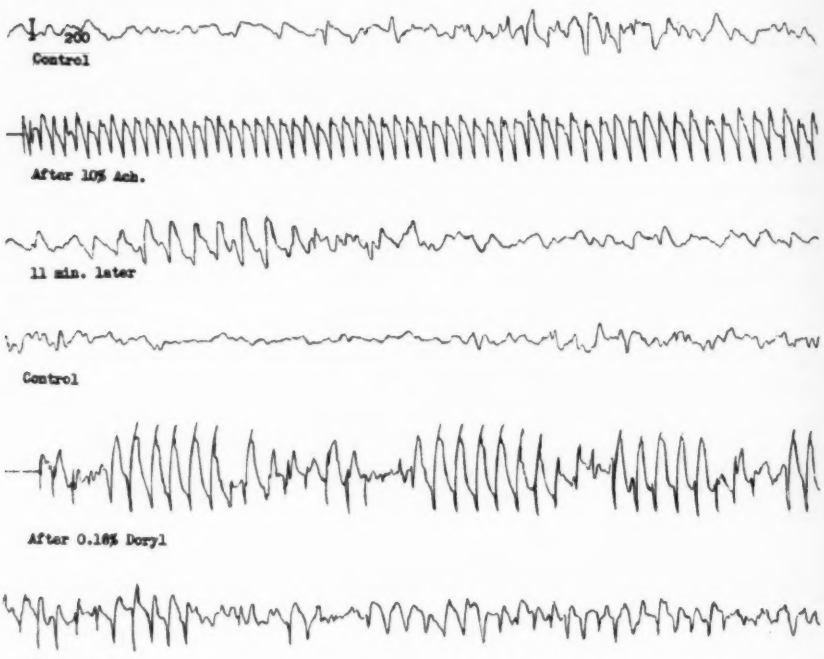

Fig. 6.—Electrical responses first to acetylcholine chloride and then to carbamylcholine chloride (doryl). Each segment represents seven seconds of record.

A definite response was obtained with solutions varying in strength from 1.25 to 5 per cent, while solutions of 0.63 per cent or less did not produce a response. The average duration of the response was about five minutes longer than that due to acetylcholine chloride.

Carbamylcholine Chloride (Doryl).—This compound also produced an electrical response in the cerebral cortex indistinguishable from that produced by the application of acetylcholine chloride (fig. 6). A marked response was regularly obtained from a 0.31 per cent solution and on one occasion a slight response was obtained from an

0.08 per cent solution. The duration of the response to carbamylcholine was much longer than that of the response to acetylcholine and was comparable to the duration of the response to a solution containing both acetylcholine and prostigmine. Such a response usually lasted more than forty minutes.

COMMENT

We have found that the application to the cat's cerebral cortex of solutions of acetylcholine chloride varying in concentration from 2.5 to 10 per cent produces a pronounced, localized increase in the electrical activity of the cortex. Miller and associates [3] have previously reported that the application of acetylcholine chloride to the physostigminized cortex in cats and rabbits is followed by the appearance of rapid, high voltage waves in the electroencephalogram, but they were unable to produce any change in the electrical activity by the application of acetylcholine chloride alone. This failure is readily explained by the fact that they used only a 1 per cent solution of the drug.

A natural question that at once arises is why it is necessary to use such high concentrations of acetylcholine chloride in order to obtain a response—concentrations that seem definitely "unphysiologic." This question, we believe, can be answered as follows:

The cerebral cortex contains an enzyme, cholinesterase, which in vitro rapidly inactivates a solution of acetylcholine by hydrolyzing it to the relatively inert choline plus acetic acid.[4] This esterase is itself quickly and completely inactivated by the presence of very small amounts of prostigmine. Acetylbetamethylcholine is somewhat more stable than acetylcholine in the presence of cholinesterase, while carbamylcholine is quite unaffected by it, behaving in this respect like a mixture of acetylcholine and prostigmine.

Table 2 shows the relation between the known stability (in vitro) in the presence of cholinesterase of the various solutions we have tested and their physiologic activity as measured (1) by the minimum concentration capable of producing an electrical response from the cortex and (2) by the duration of the response after the removal of the solution from the cortex. It is clear from the table that the less easily

3. Miller, F. R.; Stavraky, G. W., and Woonton, G. A.: Effects of Eserine, Acetylcholine and Atropine on the Electroencephalogram, Am. J. Physiol. **123**:147 (July) 1938; Effects of Eserine, Acetylcholine and Atropine on the Electrocortigram, J. Neurophysiol. **3**:131-138 (March) 1940.

4. Bernheim, F., and Bernheim, M. L. C.: Action of Drugs on Choline Esterase of the Brain, J. Pharmacol. & Exper. Therap. **57**:427-436 (Aug.) 1936. Nachmansohn, D.: Cholinesterase in Central Nervous System, Nature, London **140**:427 (Sept. 4) 1937.

the solution is hydrolyzed by cholinesterase the lower is its minimal effective concentration and the longer its effect will last.

From this we conclude that acetylcholine is actively and rapidly destroyed by the living cortex, presumably by hydrolysis to choline and acetic acid. Acetylbetamethylcholine is similarly, but less rapidly, destroyed.

A further confirmation of this conclusion is offered by our observation that if acetylcholine chloride is kept continuously in contact with the cortex instead of being removed, the electrical excitation produced will not die away in seven to fifteen minutes but will continue for at least forty minutes.

This, then, explains why it was necessary to apply such concentrated solutions of acetylcholine chloride to the cortex in order to obtain any electrical response. Acetylcholine is so rapidly destroyed

TABLE 2.—*Relation of Known Stability of Three Choline Derivatives in Various Concentrations to Their Physiologic Activity*

Drug	Stability in Presence of Esterase	Minimum Effective Concentration, Percentage	Duration of Maximal Response After Removal of Drug, Min.
Acetylcholine chloride	Very unstable	2.5	7-15
Acetylbetamethylcholine chloride	Unstable	1.25	15-25
Carbamylcholine chloride	Very stable	0.08	50+
Acetylcholine chloride and prostigmine methylsulfate	Very stable	0.05	30-90

by the cortex that relatively enormous amounts of it must be used in order that any may be left intact to produce its physiologic action. If, however, the acetylcholine is protected by the addition of prostigmine methylsulfate, which poisons the cholinesterase of the cortex, we find that solutions are effective which are from thirty to one hundred fold as dilute as before.

Early in the course of these experiments we were struck with the similarity of the records obtained by the application of these drugs to the cat's cortex to those recorded from the human cortex during convulsive seizures. Figure 7 illustrates the similarities between typical records from each source.

It goes without saying that in the present state of knowledge one cannot assert that such a superficial resemblance between two sets of electrical records means that there is necessarily a deep or far reaching similarity between the physiologic changes underlying them. In this case, however, we have a certain amount of other evidence available.

Fiamberti [5] reported that intracisternal injection of acetylcholine in man will produce generalized convulsions, and indeed he used this procedure extensively in the treatment of dementia praecox. We carried out the same procedure on cats [6] and were able to produce by this means typical, severe tonic and clonic seizures in these animals. We also confirmed Rossi's [7] observation that intravenous injection of acetyl-

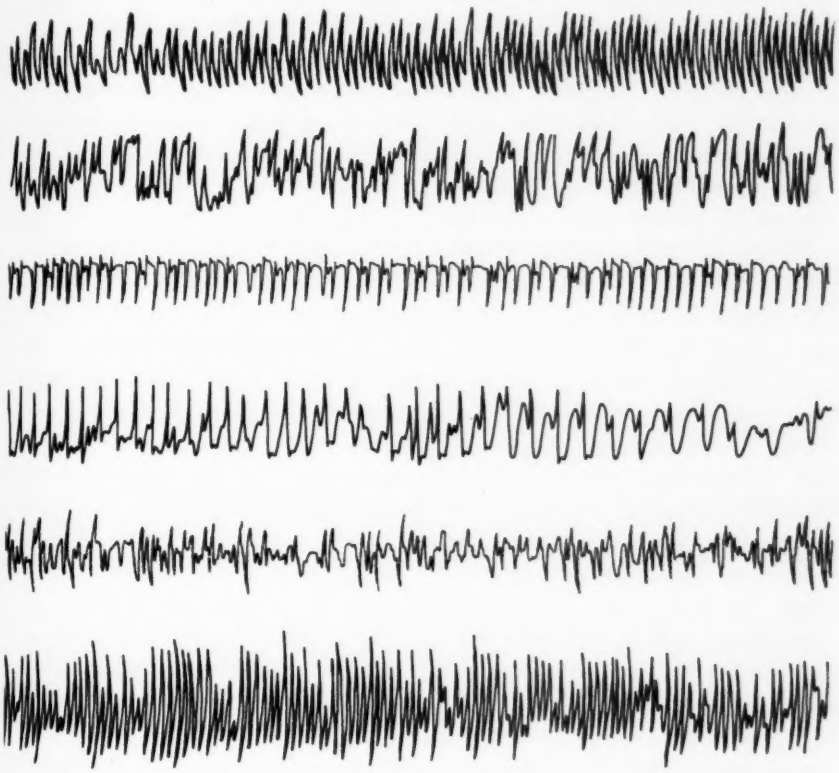

Fig. 7.—The second, fourth and sixth tracings are records of grand mal seizures in human subjects (reproduced by permission of the authors from the "Atlas of Electroencephalography," by F. A. Gibbs and E. L. Gibbs); the other three are tracings of electrical responses to acetylcholine chloride in cats. Note the similarities in form between tracings 1 and 6, 2 and 5 and 3 and 4.

choline in rabbits will produce tonic and clonic seizures. It is thus apparent that acetylcholine is a convulsant, a fact which was sug-

5. Fiamberti, A. M.: Accessi a carattere epilettico provocati con l'introduzione sottoccipitale di sostanze vasodilatrici, Riv. sper. di freniat. **61**:834-840 (Dec.) 1937.

6. Brenner, C., and Merritt, H. H.: Unpublished data.

7. Rossi, A.: Ricerche sperimentali sulle convulsioni da acetilcolina, Note e riv. di psichiat. **68**:229-239 (April) 1939.

gested by the similarity between the electrical records produced by it and those produced by spontaneous seizures. That neither focal nor generalized seizures were produced by the application of acetylcholine chloride directly to the surface of the cortex in our present series of experiments was, we feel, due to the anesthetic used. Dial was found by one of us [8] to be an extremely efficient anticonvulsant in cats, though it has not proved superior to other known anticonvulsants in the treatment of seizures in human beings.

We feel that the convulsant activity of acetylcholine is of particular importance, since it is known to be a normal constituent of the brain [9] and is believed by many to be important in, and perhaps even essential to, the normal transmission of the nerve impulse. In view of these facts, we feel justified in suggesting the possibility that disorders in acetylcholine metabolism may be of importance in the etiology or mechanism of convulsive seizures in man. Of interest in this connection is the recent report by Williams [10] that intravenous injection of acetylcholine hydrochloride was followed by increased abnormal activity in the electroencephalograms of epileptic patients.

Implicit in the line of reasoning leading to such a hypothesis is the assumption that the electrical response to acetylcholine which we have described is the result of the action of the drug on the neurons or the synapses proper. That is, we assume that its action on the cortex is analogous to that on the sympathetic ganglia and on the myoneural junction of skeletal muscle ("nicotine effect" of acetylcholine chloride). If the cortical response to acetylcholine chloride were dependent on its well known vasodilator action ("muscarine effect"), the hypothesis that alterations of acetylcholine metabolism might be of importance in the problem of convulsive seizures in human beings would be much less promising, for it seems quite unlikely, a priori, that the central nervous system would at any time produce a sufficiently high concentration of acetylcholine to influence the vascular system so profoundly.

This question as to the mode of action of acetylcholine cannot perhaps be answered with complete finality at present. In favor of the view that it acts directly on the neurons is the fact that the administration of carbon dioxide, an extremely powerful cerebral vasodilator, does not produce in man any changes in the electroencephalogram

8. Merritt, H. H.: Unpublished data.

9. Dikshit, B. B.: Acetylcholine Formation by Tissues, Quart. J. Exper. Physiol. **28**:243-251 (Nov.) 1938. Stedman, E.: Occurrence of Acetylcholine in Brain, J. Physiol. **89**:37P (April 9) 1937.

10. Williams, D.: The Effect of Cholin-Like Substances on the Cerebral Electrical Discharges in Epilepsy, J. Neurol. & Psychiat. **4**:32-47 (Jan.) 1941.

comparable to those produced in cats by acetylcholine, while Merritt and Putnam [11] found that the administration of carbon dioxide to cats actually raised their convulsive threshold.

On the other hand, there are at least two major arguments in favor of a vascular mechanism's being involved in the cortical response to acetylcholine. In the first place, Miller and associates [8] reported that the application of a 0.1 per cent solution of atropine sulfate to the physostigminized cortex altered the electrical record in a way which they interpreted as indicating that atropine antagonizes and partly inhibits the acetylcholine effect. Similarly, Henderson and Wilson [12] reported that the physiologic effects of intraventricular injection of acetylcholine in human subjects could be abolished by simultaneous intraventricular injection of atropine. In the light of present knowledge, we should expect that any direct action of acetylcholine on the cortical neurons would not be influenced by atropine while any action on the blood vessels would be so influenced, i. e., inhibited or prevented.

The second argument is based on the fact that acetylbetamethylcholine produces the same changes in the electrical record as do acetylcholine and carbamylcholine. Unlike the two latter drugs, acetylbetamethylcholine is thought to have practically only a parasympathicomimetic effect.[13] For example, Simonart [14] found that acetylbetamethylcholine was one thousand times less active in stimulating the myoneural junction of denervated skeletal muscle than was acetylcholine. If it is true that acetylbetamethylcholine in any reasonable concentrations affects only parasympathetic nerve endings, it would be fair to assume that any action it has on the cortex is due essentially to its action on the cerebral blood vessels and, by analogy, to conclude that acetylcholine and carbamylcholine, which produce apparently identical electrical changes in the cortex, act in the same way, i. e., primarily on the blood vessels.

Let us consider first the argument based on the evidence that atropine inhibits or alters the cortical response to acetylcholine. The observations

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11. Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938.

12. Henderson, W. R., and Wilson, W. C.: Intraventricular Injection of Acetylcholine and Eserine in Man, Quart. J. Exper. Physiol. **26**:83-95 (April) 1936.

13. Flexner, J., and Wright, I. S.: Effect of Acetyl-B-Methylcholine (Mecholyl) on Gastric Secretion in Animals and in Man, Am. J. Digest. Dis. **5**:736-739 (Jan.) 1939. de Wispelaere, H.: Actions de l'acétyl-B-méthylcholine, etc. sur la circulation et sur la respiration, Arch. internat. de pharmacodyn. et de thérap. **56**:363-375 (Aug.) 1937.

14. Simonart, A.: On the Action of Certain Derivatives of Choline, J. Pharmacol. & Exper. Therap. **46**:157-193 (Oct.) 1932.

of Miller and associates [3] and of Henderson and Wilson [12] were concerned with the application of solutions of atropine directly to the surface (outer or inner) of the brain. We ourselves have found that the application of a 0.5 per cent solution of atropine sulfate to the normal cortex will produce changes in the electrical record very similar to those described by Miller on atropinization of the physostigminized cortex.[6] It seems to us, therefore, that when atropine is applied directly to the brain in appreciable concentrations it has of itself a notable effect on neuronal activity, which is not to be compared with the effect of intravenous injection in the ordinary "atropinizing" dose of about 1 mg. per kilogram of body weight. Moreover, our own results show that intravenous atropinization with this dose, which should completely inhibit any vasodilator effect of acetylcholine, does not alter or prevent the cortical response to acetylcholine which is under discussion. In corroboration of this is the observation that intravenous atropinization (1 mg. per kilogram) does not prevent the convulsions produced in cats by intracisternal injection of acetylcholine chloride.[6] We should therefore take the view that the effect of acetylcholine on the electrical activity of the cortex is not greatly altered by intravenous atropinization. In this respect, therefore, it resembles the effect of acetylcholine on the sympathetic ganglion and the myoneural (skeletal) junction rather than on the parasympathetic end organ.

As for the fact that acetylbetamethylcholine produces the same changes in the electrical activity of the cortex as do acetylcholine and carbamylcholine, we have found that contraction of the nictitating membrane of the cat can, at least in some animals, be produced by perfusion of the superior cervical sympathetic ganglion with amounts of acetylbetamethylcholine as small as, or smaller than, those of acetylcholine. From this we conclude that acetylbetamethylcholine is not, in fact, without action on ganglion cells, as has hitherto been supposed.

On the basis of present knowledge, therefore, it seems to us that the three drugs here tested, acetylcholine, acetylbetamethylcholine and carbamylcholine, produce their characteristic electrical response from the cerebral cortex by direct action on the nerve cells, fibers or synapses of the cortex.

SUMMARY

The application of a 2.5 to a 10 per cent solution of acetylcholine chloride to the surface of the cat's cortex produces a pronounced increase in the electrical activity of the cortex.

This electrical response is not altered or prevented by intravenous atropinization (1 mg. of atropine sulfate per kilogram) of the animal.

Acetylbetamethylcholine chloride, carbamylcholine chloride and a mixture of acetylcholine chloride and prostigmine methylsulfate, when

applied in the same way, also produce a change in the electrical record which is indistinguishable from that produced by acetylcholine chloride.

The minimum effective concentrations and duration of effect in each case appear to be closely related to the stability of the solution in the presence of cholinesterase: The more stable the solution the lower the minimum effective concentration and the longer the effect will last.

Acetylcholine chloride appears to be rapidly destroyed by the living cortex.

It is felt that in the light of present knowledge the effect of these drugs on the cortex is comparable to the well known effect of acetylcholine chloride on the sympathetic ganglion and the myoneural junction of skeletal muscle.

Attention is drawn to the fact that acetylcholine chloride acts as a convulsant in both human beings and in cats, and to the similarities in the form and properties of the electrical activity of the cortex during convulsive seizures and after the experimental application of acetylcholine chloride.

Since acetylcholine is known to be a normal constituent of the brain and is felt by many to be important in the mediation of the nerve impulse, the facts previously cited suggest the possibility that disorders in the metabolism of acetylcholine may be concerned in the etiology or mechanism of convulsive seizures in human beings.

818 Harrison Avenue.

INTRACRANIAL AND EXTRACRANIAL VASCULAR ACCIDENTS IN MIGRAINE

HENRY S. DUNNING, M.D.
NEW YORK

Migraine is usually a benign disorder, but occasionally it is associated with serious complications involving the vascular system of the head. Such an occurrence in a private patient of mine stimulated study of the literature and the following report.

REPORT OF A CASE

A woman, born in the United States in 1904 of Polish parents, married early and gave birth to a normal child. Later, at the age of 25, both uterine tubes and one ovary were removed, for an unknown cause. Subsequently menstruation, which had begun at the age of 15, became relatively scant and lasted not longer than three days. She was sexually well adjusted. In temperament she was meticulous and exacting. Her husband spontaneously remarked: "You know, she gets very nervous; she keeps the house like a mirror; she washes the curtains every two weeks; she can't stand it if I drop cigaret ashes. Sometimes she gets so excited [about such carelessness] she gets a headache."

Apparently she inherited the tendency to headaches. Her mother, who died at the age of 50, of an unknown cause, had headaches. A sister also had headaches. The patient's headaches began during childhood, prior to menstruation. "I can remember coming home from school with a splitting headache." Occurring three or four times a month, sometimes waking her in the night, at first they were accompanied only by loss of appetite and were relieved by acetylsalicylic acid or sleep. Later, after her twenty-fifth year, they came regularly during or shortly before or after menstruation, as well as at other times, were accompanied by nausea, sometimes by vomiting, and lasted as long as two days, temporary relief being obtained only with aminopyrine or anacin.[1] Visual or other disturbances were never noted.

The most severe and persistent headache she had ever experienced began at the age of 35, on Jan. 28, 1940 (Sunday). She was waked at 9:30 a. m. by pain in the right side of the forehead, "as if somebody was twisting something there and trying to pull it out by the roots." During the day she vomited twice, and the original pain was replaced by a sensation of pressure on top of the head. With recurrence of the pain in the right side of the forehead at times, the vertex headache persisted, and on the sixth consecutive day of head discomfort, which was unyielding to aminopyrine, anacin, bromoseltzer[2] or magnesium sulfate, she

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From the Department of Medicine, New York Hospital and Cornell University Medical College.

1. Anacin, a proprietary preparation, contains acetophenetidin, acetylsalicylic acid, a caffeine alkaloid and quinine sulfate.

2. Bromoseltzer, a proprietary remedy, contains potassium bromide, acetanilid and caffeine.

consulted me. She had just vomited a small lunch, was listless, walked gingerly, as if to minimize movement at the neck, and stood somewhat unsteadily with the feet together and the eyes closed. Neurologic examination otherwise revealed nothing abnormal. She was admitted that day to the New York Hospital for further observation.

Examination of other systems revealed no abnormality except absence of the right ovary and some prolapse of the urethra. The temperature, pulse and respiration were normal. The blood pressure was 100 to 105 mm. of mercury systolic and 70 mm. diastolic. The urine was normal. The blood count revealed 93 per cent hemoglobin; 4,750,000 red cells; 8,400 white cells; 77 per cent polymorphonuclear neutrophils (9 per cent immature forms); 1 per cent eosinophils; 19 per cent lymphocytes, and 3 per cent monocytes. There was no abnormality of the red cells or platelets on smear. Urea nitrogen measured 11 mg. per hundred cubic centimeters. The Kline test for syphilis gave a negative reaction. The roentgenogram of the skull was normal. During the first twenty-four hours after admission she vomited all food, and the headache became so severe on one occasion that she wept. Three doses of codeine, 0.06 Gm. (1 grain) each, with two of which 0.6 Gm. (10 grains) of acetylsalicylic acid was given, failed to bring relief. Then analgesic medication seemed to control the headache, food was retained and she was allowed to sit in a chair forty-one hours after admission.

On February 6, the fourth day in the hospital and the second day of menstruation, an unexpected complication occurred. At 6 a. m. she reported having a slight right frontal headache and at 7:45 a. m. went to the bathroom. At 8:10 a. m. a nurse found her standing by the sink and observed "cold sweat, dribbling from the mouth and hemiplegia of the left arm and the left side of the face." There was no obvious impairment of consciousness. At 9 a. m. I found her able to give an account of her experiences in the bathroom. She had taken a shower and, while bending over to dry her legs, had felt a "shooting" pain in the right frontal region just above the hair line, which made her "dizzy." She had staggered, struck her left brow against the tile wall, regained her balance and encountered difficulty in putting on her slippers because of "numbness" of the left arm. Vomiting had not occurred. Examination revealed a small abrasion with swelling (1 cm. in diameter) of the left brow, bilateral conjunctival congestion and impairment of motility and sensory functions on the left side, as follows: decreased corneal reflex; loss of sensation to cotton and pinpoint over the face; weakness of the facial muscles during volitional movement, but not during laughter, with pronounced involvement of the lower portion, slight paralysis of the orbicularis oculi and none of the frontalis muscle; marked weakness of the tongue, with deviation to the left on protrusion; decreased amplitude of alternating movements of the arm and leg; decreased superficial abdominal reflex; ankle clonus, of one jerk; loss of sensation to cotton, pinpoint and passive movement of the joints of the arm and leg (trunk not tested), and decreased sensation to squeezing the calf. At 10:30 a. m. I performed lumbar puncture with a no. 22 needle. The initial resting pressure was 165 mm. of spinal fluid (with the patient in the horizontal position). About 18 cc. of fluid was collected in eight test tubes, in each of which it was blood tinged to an equal degree. The cell count on fluid in the eighth tube, containing the last few drops of fluid withdrawn, was as follows: 4,000 red blood cells and 50 white blood cells per cubic millimeter, 92 per cent mononuclears and 8 per cent polymorphonuclears. Cleared of cells by centrifuging, the fluid was xanthochromic. Culture of the fluid was sterile. A roentgenogram of the skull revealed no fracture.

Improvement was continuous. Twenty-four hours after the hemorrhage the sensation of numbness on the left side was less, and the patient was able to differentiate between the point and the head of a pin on the left hand. During convalescence quantitative olfactory function (Elsberg's method) and visual fields as plotted on the perimeter and the wall screen were normal. Lumbar puncture was repeated with a 22 caliber needle nine days after the first. The initial resting pressure was 150 mm. of spinal fluid (with the patient in the horizontal position). The fluid was watery and clear. A cell count revealed 21 white blood cells per cubic millimeter, all of which were mononuclears, and no red blood cells. The total protein was 50 mg. per hundred cubic centimeters. The colloidal gold curve was 1121000000. The Wassermann reaction was negative. Slight pain in the right frontal region, just above the hair line, persisted for nine days. Then, a week later, one of her usual headaches recurred in a setting of annoyance. Having been kept awake during the night by noise, the following morning she had mild bilateral frontal pain, which grew worse during the visit of her sister-in-law, who intimated that she was getting an undeserved rest in a hospital for such an ordinary ailment as headache. After this visit the patient vomited, and the pain ceased after analgesic medication. She was discharged from the hospital on February 23, with the following impairment of function on the left side: slight decrease in the corneal reflex and in corneal sensation, slight weakness of the lower facial muscles, slight weakness of the tongue and loss of the superficial abdominal reflex. At no time had there been any abnormality of the optic fundi.

The diagnosis was migraine, with right cerebral hemorrhage.

I examined the patient on nine occasions, up to a year and a half after discharge from the hospital. Recovery of function was not quite complete. She complained of not being aware of liquid drooling from the left corner of the mouth while eating, of unpleasant hypersensitiveness to touch over the left side of the face and the left arm and leg and of tingling of the left hand and foot on prolonged use. Neurologic examination revealed alterations of sensation on the left side as follows: slightly decreased corneal sensation; impairment of two point discrimination on the lower lip, and unpleasant hypersensitiveness of the face, arm and leg to stroking with the finger tips. All other sensory functions were normal, including two point discrimination at 1 cm. on the finger tips, and there was no motility defect. The blood pressure remained normal. Headaches accompanied by nausea, and sometimes by vomiting, continued with their usual frequency, relation to menstruation and response to analgesic medication, but were almost always limited to one or the other side of the forehead and lasted no longer than twenty-four hours. They occurred more often on the right, but the attacks on the left were more severe. The pain was throbbing in quality.

COMMENT

According to Riley,[3] Aretaeus of Cappadocia, at the end of the first century A. D., isolated from the general group of headaches a particular type characterized by its paroxysmal severity, its one sidedness, its association with nausea and its more or less regular recurrence, the crises of pain being separated by intervals in which the patient is free from all discomfort. The essential features of the migraine syndrome are thus simply stated. Unmistakable signs of transient neural dysfunction may be associated with the headache. These manifestations

3. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429 (Nov.) 1932.

are homonymous hemianopia with scintillations, hemiparesthesia, aphasia and hemiplegia, indicating cerebral involvement, and unilateral scotoma, indicating involvement of the optic nerve or the retina. Other visual disturbances mentioned by Grönvall [4] are bright or colored spots and dimness of vision in one eye or the other which may develop into complete blindness for a time. Such transient neural dysfunction usually precedes the headache and is relatively brief, but I have examined a patient with migraine whose homonymous hemianopia regularly persists throughout the period of pain, for as long as six hours. Ocular paralysis is sometimes included among the transient neural dysfunctions associated with the headache, but Riley [3] offered evidence suggesting that so-called ophthalmoplegic migraine has a definite individuality. He cited 5 cases so diagnosed clinically in which the oculomotor nerve was observed at autopsy to be involved by an aneurysm or an inflammatory or neoplastic lesion. He also stated that the ophthalmoplegia may develop in the course of simple migraine which has been well established for many years and, in contrast to the other associated phenomena, usually appears with the subsidence of the headache and is persistent, tending to remain at least two days, or even permanently. Possibly ocular paralysis of this nature is in some instances a complication of migraine rather than one of its symptoms.

There is evidence that the headache and neural dysfunction associated with migraine are vascular in origin. Thus, Graham and Wolff [5] demonstrated that the headache is probably caused by distention of cranial arteries. They also noted concomitant prominence of cranial veins. As to neural dysfunction, Schumacher and Wolff [6] presented observations indicating that cerebral vasoconstriction was responsible for the homonymous quadrantic hemianopia in a patient with migraine.

On the basis of such demonstrable abnormal physiology, it requires no stretch of the imagination to suppose that vascular accidents about the head occur during attacks of migraine. Study of the literature reveals the truth of this supposition. The case here described resembles others that have been reported as examples of the complications occasionally occurring in migraine. These mishaps consist of rupture or occlusion of intracranial or extracranial blood vessels with persistent sequelae due to hemorrhage or infarction. There are several case reports bearing the inference that the migraine disorder was thereby the cause of serious injury to nerve tissue, with resulting persistent homonymous hemianopia, unilateral scotoma, aphasia, hemiplegia or

4. Grönvall, H.: On Changes in the Fundus Oculi and Persisting Injuries to the Eye in Migraine, Acta ophth. **16**:602, 1938.

5. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, Arch. Neurol. & Psychiat. **39**:737 (April) 1938.

6. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache, Arch. Neurol. & Psychiat. **45**:199 (Feb.) 1941.

hemianesthesia. The validity of this inference, however, is in some instances weakened by lack of autopsy or follow-up data and such details essential to the study of vascular disorders as the age of the patient, the blood pressure, the condition of the blood and the reactions for syphilis and the inclusion of persons within the age period in which there is a tendency to arteriosclerosis. It is probable that distention or constriction of cranial arteries known to occur during attacks of migraine precipitates rupture or occlusion at the site of an aneurysm or arteriosclerotic narrowing, a circumstance in which the migraine disorder would be only a contributory cause. In the following review of the literature emphasis is placed on case reports concerning persons believed to be normal except for migraine and giving some tangible evidence of the pathologic nature of the complications. Even in such instances it is only presumptive that no latent structural lesions of the cranial blood vessels existed.

In 1881 Féré [7] stated that Charcot expressed his belief that any of the transient neural dysfunctions of ophthalmic migraine, such as hemianopia, aphasia, sensory disorders and paralyses, could become permanent. Féré [8] postulated that cerebral blood vessels temporarily spastic during attacks of migraine might become permanently constricted and eventually thrombosed, thus causing infarction. In 1907 Thomas [9] pointed out that persistence of such losses of function is not necessarily confined to those cases of migraine in which they have been transitory; he reviewed and evaluated the literature on these complications and reported 2 cases of persistent homonymous hemianopia in which "we can ascribe the cerebral softening to nothing else than an attack of migraine."

Included among Thomas' references, but not mentioned in the text, is a case reported by Brasch and Levinsohn [10] in 1898, in which direct observation on the pathologic nature of the complications of migraine were possible. The report concerned a man of 23, who, during a period of almost two years, had five attacks of migraine. In three of them pain in the left side of the forehead was accompanied by hemorrhage in the region of the orbit on that side. In the first attack there was ecchymosis of the lower eyelid; in the second, infiltration of

7. Féré, C.: Contribution à l'étude de la migraine ophtalmique, Rev. de méd., Paris **1**:625 (Aug.) 1881.

8. Féré, C.: Note sur un cas de migraine ophtalmique à accès répétés et suivis de mort, Rev. de méd., Paris **3**:194, 1883.

9. Thomas, J. J.: Migraine and Hemianopsia, J. Nerv. & Ment. Dis. **34**:153 (March) 1907.

10. Brasch, M., and Levinsohn, G.: Ein Fall von Migräne mit Blutungen in die Augenhöhle während des Anfalls, Klin. Wchnschr. **35**:1146 (Dec. 26) 1898.

both eyelids with blood, and in the third, hemorrhage into the eyelids, conjunctiva and retina, the retinal lesion causing temporary blindness in the left eye. These accidents occurred during vomiting or while he was on the toilet at the time of the headache.

Further information on the complications of migraine is found in a monograph by Flatau [11] (1912). With respect to extracranial hemorrhage, of special interest is the citation from Tissot, who, as long ago as 1813, observed at the height of the migraine attack distention of the temporal artery, congestion of the face, reddening of the eyes and extravasation of blood into the forehead and eyelids. Flatau mentioned a case of his own, that of a woman of 27 who had nosebleed before and during her migraine attacks.

In 1915 Hunt [12] reported 8 cases of migraine in which persistent sequelae had developed. These complications were ocular palsies, homonymous hemianopia, hemiplegia and optic neuritis. His patient with hemiplegia was treated at the New York hospital, and the case so closely resembled mine that further information was obtained from the hospital record and by follow-up inquiries. During childhood this patient began to have headaches, most severe in the occipital region, which usually terminated in nausea and vomiting. Her mother and other members of the maternal line also had migraine. In 1912, at the age of 32, during the night of the third day of menstruation, she had an attack of severe occipital headache, rose from bed in order to vomit and fainted. The following day she was admitted to the New York Hospital in a semiconscious state. There were left hemiplegia involving the face, tongue, arm and leg, left hemianopia, slight stiffness of the neck, slight bilateral papilledema and fresh blood in the spinal fluid on five occasions. Except for polymorphonuclear leukocytosis, the other results of studies, including examination of the heart, blood pressure determinations and Wassermann tests of the blood and spinal fluid, were normal. She made a complete recovery. The physician who last attended her reported that she died 18 years later, in 1930, at the age of 50, of chronic myocarditis complicated by auricular fibrillation and pleural effusion, having had no migraine attacks during the last ten years of her life. Thus, there is no evidence in the subsequent history of this patient which would disprove Hunt's inference that the cerebral hemorrhage was caused by an attack of migraine.

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11. Flatau, E.: Die Migräne, in Alzheimer, A., and Lewandowsky, M.: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1912, nos. 1-3.

12. Hunt, J. R.: A Contribution to the Paralytic and Other Persistent Sequelae of Migraine, Am. J. M. Sc. **150**:313 (Sept.) 1915.

Since Hunt's article several other papers on the subject under consideration have appeared. Wiener [13] (1921) reported a case of permanent homonymous hemianopia in a woman of 40 following an attack of migraine. Goldflam [14] (1923) included migraine among the causes of spontaneous subarachnoid hemorrhage. Adie [15] (1930) reported 6 cases of permanent homonymous hemianopia associated with migraine. Bonhoeffer [16] (1940) described the case of a woman who at 27 had evidence of persistent neural defects on the right, consisting of impairment of position sense and stereognosis in the fingers, slight weakness of the lower portion of the face and suggestive signs of pyramidal involvement in the forearm. For five years she had suffered from headaches associated with transient impairment of vision and speech and right hemiparesthesia. The results of air encephalography were without significance. In 4 cases reported during this period direct observations on the pathologic nature of the complications of migraine were possible, and for this reason they are reviewed in greater detail.

In 1922 Löhlein [17] reported the case of a man who had been blinded by migraine. This patient suffered after his twentieth year from severe frontotemporal headaches associated with dimness of the whole visual field, followed by transient blindness. The attack ended with vomiting. At the age of 37 an attack with vomiting occurred during the night. The following morning he noted blindness of the left eye, which was due to a large hemorrhage into the optic nerve. After resorption the nerve became atrophic, and the extent of visual recovery was limited to recognition of a finger in a small peripheral portion of the field. At the age of 42 a similar attack with severe retching occurred during the night. The following morning he noted blindness of the right eye, which was complete except for recognition of the hand in the peripheral field. Examination revealed extensive hemorrhage into the retina and vitreous. With resorption there was considerable improvement in the field, and central vision advanced to one-fifth normal. His health was otherwise sound. In 1926 Wegner [18] reported that in connection

13. Wiener, A.: A Case of Permanent Homonymous Hemianopsia Following an Attack of Migraine, M. Rec. **100**:849 (Nov. 12) 1921.

14. Goldflam, S.: Beitrag zur Aetiologie und Symptomatologie der spontanen, subarachnoidalen Blutungen, Deutsche Ztschr. f. Nervenh. **76**:158, 1923.

15. Adie, W. J.: Permanent Hemianopia in Migraine and Subarachnoid Hemorrhage, Lancet **2**:237 (Aug. 2) 1930.

16. Bonhoeffer, K.: Dauerausfallsercheinungen bei Migräne, Deutsche med. Wchnschr. **66**:521 (May 10) 1940.

17. Löhlein, W.: Erblindung durch Migräne, Deutsche med. Wchnschr. **48**:1408 (Oct. 20) 1922.

18. Wegner, W.: Augenspiegelbefunde bei Migräne, Klin. Monatsbl. f. Augenh. **76**:194 (Feb.) 1926.

with another attack of migraine this patient, at the age of 46, sustained a large hemorrhage into the right optic nerve, followed by its atrophy and blindness of the right eye even to light.

In 1934 Peters [19] reported the case of a woman who died suddenly at the age of 25 of an intracranial hemorrhage during the first day of menstruation. The only significant lesion observed at autopsy was a red focus of cerebral softening the size of a large hen's egg in the floor of the left lateral ventricle. Blood had escaped from this lesion to fill the entire ventricular system. Gross and microscopic study revealed no rupture or other abnormality of the blood vessels. There was a history of headaches during childhood, which ceased for a time and then recurred at the age of 21. Usually beginning the day before menstruation, they were at first occipital, later in the attack became generalized and were associated with severe backache, scintillations, photophobia and vomiting. During the four years prior to her death she was admitted on three occasions to a municipal hospital in Wiesbaden, Germany, where the clinical observations were remarkably complete. They included data on three menstrual periods, with headache, stiff neck and fever. During one of these attacks fluid obtained by lumbar puncture contained a slight amount of blood, which was said to be *artifiziell*. One month before death, when the patient had no complaints, fluid obtained by cisternal puncture was clear; the cell count was "10/3"; pressure was not increased; the Nonne, Pandy and Wassermann reactions were negative, and the colloidal gold curve was normal.

In 1937 Vallery-Radot, Blamoutier, Mauvas and Hamburger [20] reported the case of a woman of 35 who had a retinal hemorrhage after an attack of migraine during the seventh month of this disorder. The attacks began with a partially blind spot and bright and colored streaks. The visual phenomenon lasted ten to fifteen minutes and was followed by right or left frontal headache of several hours' duration, with hypersensitivity to noise and light, vertigo, nausea and often vomiting. At first occurring only once a month, the attacks increased in frequency to once a week. On the second day after the last of a series of three attacks at intervals of only two days she waked in the morning with a completely blind spot in the field of the left eye. This defect persisted and was not accompanied by headache. Examination a week later revealed in the visual field of this eye a scotoma near the fixation point, corresponding to a retinal hemorrhage in the macular region about three times as large

19. Peters, R.: Tödliche Gehirnblutung bei menstrueller Migräne, Beitr. z. path. Anat. u. z. allg. Path. **93**:209, 1934.

20. Vallery-Radot, P.; Blamoutier, P.; Mauvas, L., and Hamburger, J.: Accès de migraine ophtalmique suivis d'une hémorrhagie rétinienne, Ann. de méd. **41**:132 (June) 1937.

as the optic disk. The eye was otherwise normal. Other examinations, including studies of the blood pressure, blood and spinal fluid and Wassermann tests of the blood and the spinal fluid, elicited no explanation for the hemorrhage. After this complication the patient was observed for over three years. After resorption of the hemorrhage the retina appeared normal. The usual attacks of migraine continued, but with diminished frequency and discomfort. In concluding, the authors raised the question whether a vasomotor phenomenon such as occurs in migraine could be the cause of hemorrhage in a young woman without arterial hypertension or sclerosis.

In contrast to the pathologic process observed in the last case, Grönvall[4] (1938) reported a retinal infarction in a girl of 18 who suffered from migraine subsequent to the onset of menstruation, at the age of 12 or 13. The attacks began with large grayish white patches outlined in color in the visual field. Sometimes this symptom was replaced or accompanied by giddiness. Clearing of vision after one to five minutes was followed by severe headache beginning in one temple or at the root of the nose and becoming bitemporal. The pain lasted an hour to a day and was accompanied by nausea, and at times by repeated vomiting. The attacks usually having occurred in this manner once or twice a month, the visual disturbance or the giddiness tended to occur without the other symptoms for more than a year. Then, within a period of twenty-four hours she had two attacks of giddiness. The second was accompanied by the usual visual disturbance, which, instead of clearing, led to blindness of the right eye. Complete at first, about ten minutes later she was able to see objects in the lower half of the field. There was no headache. Examination of the affected eye the next day revealed a defect in the upper half of the field, corresponding to edema of the lower half of the retina. The inferior temporal artery of the retina was slightly narrowed and one branch was so thin it could hardly be traced. Other examinations, including neurologic tests, roentgenographic studies of the skull and the Wassermann test of the blood, gave normal results. Blood pressure was 145 mm. of mercury systolic and 85 mm. diastolic. The retinal edema completely subsided, but at the time of the last reported examination, nine weeks after the infarction, the arterial narrowing was still present and there was only slight improvement in the visual field. The author expressed the belief that arterial spasms in the retina, which had caused the transient visual disturbances, had finally led to such changes in the intima that persistent constriction resulted.

In the case herein reported and in others summarized from the literature there is evidence that physical activity during the migraine

headache precipitated hemorrhage. Out of a total of 10 instances of hemorrhage, such evidence is found in 7. Thus, 5 hemorrhages, 3 ocular (case of Brasch and Levinsohn) and 2 cerebral (case of Hunt and my case), occurred during the headache at the time of vomiting, straining at stool (presumably) or bending over to dry the legs. The other 2, both ocular hemorrhages (case of Löhlein), were discovered shortly after vomiting or retching during the headache. All of these acts cause distention of cranial veins, and, according to Hamilton, Woodbury and Harper,[21] the exertions that raise pressure within the abdominal and thoracic cavities cause an increase in pressure within cranial arteries. These authors stated:

> These very large increases in arterial pressure on coughing and straining put a degree of stress on the arterial tree and give rise no doubt to interstitial hemorrhages. Because of their serious consequences, such hemorrhages have received particular attention when they occur within the craniospinal canal.

Since it is known that cranial arteries and veins are distended during migraine headache, it is conceivable that sudden further stretching might cause rupture.

SUMMARY

A case of migraine in which a cerebral hemorrhage occurred during an attack is reported and the relevant literature reviewed, with emphasis on the report of 6 cases. The subsequent history in 1 of the cases has been obtained. Including the case herein reported and those in the literature, 7 cases of migraine with intracranial or extracranial vascular accidents are considered. Five of the patients were females and 2 were males, and all were within the age period of 18 to 37 years at the time of the first accident. With the exception of my patient, who had an irrelevant pelvic condition, all were considered in normal health except for migraine. There were 11 vascular accidents in all, only 1 causing death. Except for a retinal infarction, all were hemorrhages. Of the 10 hemorrhages, 7 involved the eye and were directly observed. The other 3 were cerebral, of which 2 were detected by the presence of blood in the spinal fluid; the other was directly observed at autopsy. Three hemorrhages, all cerebral, occurred during menstruation. Five hemorrhages, 3 ocular and 2 cerebral, occurred at the time of headache and were precipitated by activity producing sudden increase in pressure within the blood vessels of the head. Two other hemorrhages, both ocular, were discovered a short time after such activity during the headache.

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21. Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Physiologic Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853 (Sept. 12) 1936.

CONCLUSIONS

On the basis of the case herein reported and the data found in the literature, the following conclusions seem justified:

1. Migraine in persons considered otherwise normal is occasionally associated with intracranial and extracranial vascular accidents.

2. Changes in caliber of cranial blood vessels known to occur during attacks of migraine are probably predisposing factors in hemorrhage and occlusion.

3. Activity producing sudden increase in pressure within the blood vessels of the head during the migraine headache is a precipitating factor in hemorrhage.

4. Unless such vascular accidents can be attributed to latent structural lesions of cranial blood vessels, migraine should be regarded as an instance of disordered function capable of causing irreversible tissue change.

New York Hospital.

WATER METABOLISM IN RELATION TO CONVULSIONS

II. SPECIFIC GRAVITY OF BLOOD AND BLOOD SERUM

THEODORE T. STONE, M.D.

ALEX J. ARIEFF, M.D.

AND

JOSEPH A. LUHAN, M.D.

CHICAGO

Previously, one of us (T. T. S.) and an associate [1] reported on a study of water balance in 18 young adults suffering from convulsions. Two of the five conclusions in the former paper will be restated here, since they led to the present study. 1. It is extremely difficult with the present methods of examination, to demonstrate a state of positive water balance in the adult human subject by excessive oral intake of fluid, even when supplemented by antidiuretic measures. 2. There was no evidence from our study to support the contention that in the adult epileptic patient the body fluid reaches a high peak just before a convulsion, drops during the seizure and rises again as a result of water retention. Furthermore, it is our opinion, expressed at that time, that either the methods for examination of body fluids were so variable as to be unsuitable for our purpose or it was almost impossible to hydrate a subject by means of oral intake of large quantities of water within a short interval with or without antidiuretic measures. It was decided, therefore, to employ measurements of the specific gravity of the whole blood or the blood serum after the oral intake of water as a possible index of resultant change in the water content of the blood.

Our present investigation was undertaken to determine whether the drinking of 2,000 cc. of water in fifteen to thirty minutes by a patient suffering from epilepsy with recurrent convulsions produces a state of hydration. The method of Barbour and Hamilton [2] and that of Kagan [3] were used in the determinations of specific gravity.

This study was aided by a grant from the Minnie Frances Kleman Memorial Fund.

From the Department of Nervous and Mental Diseases, Northwestern University Medical School.

1. Stone, T. T., and Chor, H.: Water Metabolism in Relation to Convulsions, Arch. Neurol & Psychiat. **38**:798 (Oct.) 1937.

(Footnotes continued on next page)

METHODS AND MATERIAL

The principle of the Barbour and Hamilton procedure involves timing the fall of a drop of body fluid (blood) of known size through a definite distance in a mixture immiscible with the fluid. This mixture should have a low viscosity and a specific gravity somewhat below that of the fluid to be tested. It consists of two substances, one heavier and one lighter than the range of fluids to be tested, so that by adjusting the proportions the specific gravity of the mixture can be adapted to the expected conditions. Two satisfactory substances of sufficiently low volatility and viscosity used are xylene and bromobenzene. A standard solution of potassium sulfate of known density is used as a standard for comparison. The proper mixture of xylene and bromobenzene is held in a tube of standard bore immersed in a water bath the temperature of which is determined. Just below the surface of this mixture a drop of blood of exactly 10 cu. mm. is released from the pipet. The falling time for a distance of 30 cm. is determined by means of a stopwatch. With the aid of a nomogram or an alinement chart, one determines from the temperature and falling time the apparent difference in density between the blood or the standard and the solution through which it falls. The true difference in density between the blood and the standard is then either added to or subtracted from the specific gravity of the standard solution, according to which fell faster.

The Kagan proteinometer[4] consists of an outer glass cylinder, acting as a water bath, and an inner tube of a certain uniform bore, which bears two graduated scales. A thermometer projects in the water bath around the inner tube. The central tube is filled with a standardized oil (a mixture of methyl salicylate and liquid petrolatum), supplied with the instrument. A drop of blood serum of constant size is delivered by means of a special dropping pipet and released below the surface of the oil in the calibrated tube, and its falling time between two graduations is measured with the aid of a stopwatch. By the use of a table, observed falling times are converted to specific gravities and corrected to the values obtaining at 25 C. when the actual temperature differs therefrom (within the range of 20 to 30 C.). Kagan's method does not require timing of the falling of a drop of liquid of known specific gravity, as is required in the original procedure of Barbour and Hamilton.

Forty-one patients were thus studied. Ten were ambulatory and were tested in the clinic, while 31 were hospitalized and were examined there. The specific gravity of the whole blood was determined on the 10 ambulatory patients, while the specific gravity of the blood serum was determined on the 31 hospitalized patients. Two control specimens from each patient of the two groups were taken and examined prior to the beginning of the test. Two thousand cubic centimeters of water was drunk by each patient in each group in a period of fifteen to thirty

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2. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625, 1926.

3. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: I. A Falling Drop Method for the Determination of Specific Gravity, J. Clin. Investigation **17**:369, 1938; II. The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, ibid. **17**:373, 1938.

4. Obtainable from E. H. Sargent & Co., Chicago.

minutes. From the 10 ambulatory patients specimens of blood were taken fifteen, thirty and ninety minutes after the drinking of the water and the specific gravities were determined. From the 31 hospital patients specimens of blood were removed thirty, sixty and one hundred and twenty minutes after the drinking of the water and the serum was tested for its specific gravity. In the hospitalized group pitressin was given hypodermically before and after the drinking of the water. Forty of our 41 patients were receiving anticonvulsant medication.

RESULTS

Ambulatory Patients (table 1).—The greatest average decrease in specific gravity occurred ninety minutes after ingestion of water and

TABLE 1.—*Specific Gravity of Whole Blood, Referred to 25 C., As Determined on Ten Ambulatory Patients with Epilepsy*

Patient No.	Name	Age, Yr.	Sex	Type of Epilepsy *	Weight, Lb.	Specific Gravity			
						Initial	Control Determination 15 Min. Later	15 to 30 Min. After Drinking Water	90 Min. After Drinking Water
1	A. J.	27	M	OPG	132	1.0665	1.0663	1.0661	1.0661
2	C. S.	32	M	IPG	153	1.0690	1.0690	1.0690	1.0690
3	J. G.	29	M	IPG	129	1.0597	1.0589	1.0584	1.0584
4	C. R.	53	M	OPG	138	1.0671	1.0677	1.0671	1.0671
5	R. G.	32	M	FG	128	1.0686	1.0686	1.0673	1.0673
6	E. C.	32	M	OG	154	1.0579	1.0579	1.0568	1.0565
7	C. K.	20	M	IPG	170	1.0578	1.0578	1.0562	1.0579
8	J. K.	49	M	OPG	147	1,0565	1.0565	1.0562	1.0562
9	W. T.	52	M	IG	125	1.0565	1.0565	1.0552	1.0537
10	A. S.	40	M	FG	122	1.0627	1.0626	1.0610	1.0590
Mean, with its probable error.....						1.0622 ± 0.0011	1.0622 ± 0.0011	1.0613 ± 0.0012	1.0611 ± 0.0012

Probable error of the mean was calculated by the formula:

$$\text{P.E.}_{\bar{x}} = \pm 0.6745 \sqrt{\frac{S(x - \bar{x})^2}{n(n-1)}}$$

* I indicates idiopathic; O, organic; F, focal; P, petit mal; G, grand mal, and OPG, organic with both petit and grand mal.

amounted to a decrease of 0.0011. This difference is less than its probable error (± 0.0016) and hence is not statistically significant, a mathematical consequence which might have been expected from inspection of the values in the table, in view of the small number of cases studied and an inconstant response of small magnitude as compared with the initial range of the specific gravities of the blood. One patient in this series, W. T., aged 52, had a grand mal attack just after the specific gravity had decreased in thirty minutes from 1.0565 to 1.0552, and an hour later, after the effects of the attack had practically worn off, showed still greater lowering of the specific gravity (0.0028 below the initial reading). He was the only one in the entire series of 41

patients who had a seizure during the course of the determinations. Another patient in this series, A. S., showed a considerable drop in the specific gravity of the blood after ninety minutes, amounting to 0.0037.

Hospitalized Patients (table 2 and chart).—The specific gravity in the control specimens ranged from 1.0216 to 1.0300. Thirty minutes

TABLE 2.—*Specific Gravity of Serum, Referred to 25 C., as Determined By the Kagan Proteinometer on Thirty-One Hospitalized Patients with Epilepsy*

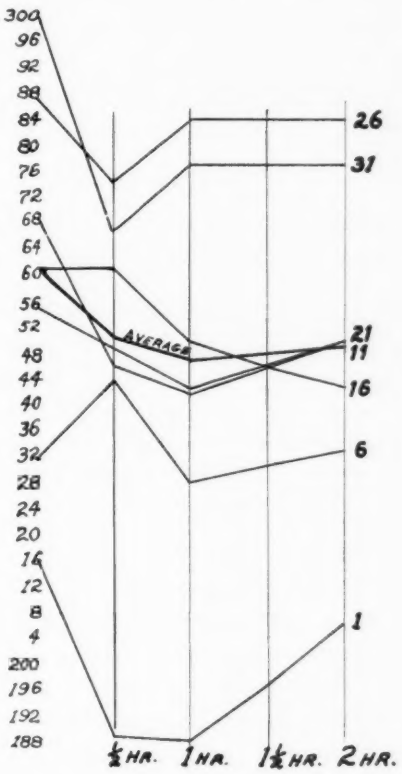
Patient No.	Name	Age, Yr.	Sex	Type of Epilepsy *	Weight, Lb.	Specific Gravity			
						Initial	½ Hour After Ingestion of Water	1 Hour After Ingestion of Water	2 Hours After Ingestion of Water
1	M. S.	27	F	FG	132	1.0216	1.0189	1.0188	1.0206
2	N. M.	54	F	FPG	103	1.0226	1.0213	1.0207	1.0236
3	A. B.	53	M	OPG	155	1.0229	1.0224	1.0222	1.0228
4	R. H.	15	M	IPG	125	1.0230	1.0229	1.0230	1.0221
5	F. K.	38	M	IPG	167	1.0232	1.0224	1.0223	1.0240
6	C. P.	38	F	IG	171	1.0232	1.0244	1.0228	1.0233
7	C. W.	11	F	FG	90	1.0239	1.0239	1.0237	1.0244
8	D. S.	17	F	IG	122	1.0241	1.0224	1.0226	1.0228
9	A. R.	24	F	IPG	93	1.0250	1.0236	1.0236	1.0238
10	J. C.	12	M	IPG	87	1.0254	1.0237	1.0237	1.0260
11	H. M.	53	M	IB	164	1.0255	.....	1.0243	1.0250
12	L. M.	32	F	IPG	145	1.0256	1.0249	1.0243	1.0241
13	J. L.	37	F	IPG	146	1.0258	1.0254	1.0249	1.0248
14	M. G.	21	F	IPG	131	1.0259	1.0257	1.0253	1.0259
15	M. H.	39	M	IPG	161	1.0259	1.0259	1.0246	1.0237
16	C. L.	16	M	IPG	116	1.0261	1.0261	1.0250	1.0243
17	W. H.	17	M	FPG	117	1.0262	1.0241	1.0240	1.0247
18	R. Y.	22	M	IG	143	1.0264	1.0258	1.0240	1.0241
19	H. W.	14	M	OP	93	1.0264	1.0237	1.0248	1.0254
20	H. O.	38	M	IPG	114	1.0265	1.0266	1.0259	1.0254
21	K. S.	12	M	OPG	65	1.0269	1.0246	1.0242	1.0250
22	E. J.	17	M	IPG	146	1.0277	1.0251	1.0250	1.0243
23	O. G.	30	M	IPG	151	1.0277	1.0286	1.0272	1.0273
24	C. D.	9	M	IG	65	1.0280	1.0260	1.0268	1.0274
25	C. K.	39	F	IPG	160	1.0285	1.0255	1.0261	1.0259
26	E. Mc.	28	F	IG	184	1.0287	1.0274	1.0284	1.0284
27	M. P.	35	M	IPG	99	1.0288	1.0260	1.0260	1.0277
28	D. T.	18	M	IG	152	1.0290	1.0269	1.0266	1.0272
29	R. B.	8	M	IPG	55	1.0291	1.0276	1.0290	1.0257
30	P. D.	31	F	IG	159	1.0294	1.0303	1.0282	1.0290
31	W. R.	14	M	IPG	76	1.0300	1.0267	1.0277	1.0277
Mean, with its probable error.....						1.02610 ± 0.00027	1.02496 ± 0.00028	1.002468 ± 0.00027	1.02505 ± 0.00023

* F indicates focal; G, grand mal; I, idiopathic; P, petit mal, and O, organic.

after the oral intake of 2,000 cc. of water the readings varied from 1.0189 to 1.0303. The change was from 0.068 to 0.320 of 1 per cent. Four of 31 patients had higher specific gravities at this time than at the initial readings. Sixty minutes after ingestion of water the values ranged from 1.0188 to 1.0290. The changes with respect to the basal reading ranged from 0.01 to 0.28 of 1 per cent. One hundred and twenty minutes after the beginning of the test the specific gravities

ranged from 1.0206 to 1.0290. The change, therefore, was from 0.01 to 0.33 of 1 per cent. In 5 cases at this period the specific gravity of the blood was greater than at the beginning of the experiment.

The greatest average change, a decrease, in the specific gravity of the blood serum occurred one hour after intake of 2,000 cc. of water and amounted to 0.0014. This difference is 3.7 times its probable error, not quite statistically significant, since a difference of less than 4.0 times its probable error might arise through chance.[5]



Graphic representation of the specific gravity in every fifth case of the 31 cases studied. (See table 2 for cases 1, 6, 11, 16, 21, 26 and 31.)

5. The critical ratio of 3.7 in this case, simply expressed, signifies that if this study were repeated under the same conditions one hundred times the probable occurrence purely through chance of an average deviation as great as or greater than 0.0014 from the initial value would be 1.28 times (corresponding to odds of 78.53 to 1). For a difference to be statistically valid one ordinarily demands that this difference divided by its probable error be 4.0 or greater. With a critical ratio of 4.0, the odds against the occurrence of a difference as great as or greater than the one under consideration arising from chance are 142.3 to 1 (Pearl, R.: Medical Biometry and Statistics, ed. 3, Philadelphia, W. B. Saunders Company, 1940, p. 472).

There is a close, straight line relationship between the specific gravity and the protein content of the plasma and serum.[6] By means of the conversion formula used by Kagan ($P = 345\ [G - 1.0076]$), in which P denotes the total grams of protein per hundred cubic centimeters of serum and G, the specific gravity, one can translate the values for specific gravity into measures of the total protein content of the blood.

If one accepts the means of each column of values as representing the best available criterion of the trend in these values for specific gravity of the blood serum after ingestion of water, it follows that the maximum average decrease in specific gravity corresponds to a diminution in the total protein content of the serum of from 6.38 Gm. per hundred cubic centimeters (specific gravity, 1.0261) to 5.90 Gm. (specific gravity, 1.0247).

COMMENT

Accepting the difference between the most widely differing means of the several groups of values at given intervals after water intake as the best available indication of the usual change in specific gravity to be expected after ingestion of 2,000 cc. of water by a patient suffering from recurrent convulsions, one is faced with the problem of evaluating the significance of this difference. The difficulty is enhanced by lack of exact knowledge of the total blood volume at various intervals after the ingestion of large quantities of fluid. Then, too, as Heller and Smirk[7] pointed out, when one speaks of blood dilution, it is necessary to state the substance used as an index of dilution and the nature of diluent.

It must be emphasized that this method furnishes an indirect measure of the protein content of the serum of considerable validity but does not directly measure the water content of the serum. By inference one could expect that the change in water content corresponding to a decrease in proteins of from 6.4 to 5.9 Gm. per hundred cubic centimeters would be an increase of comparable magnitude (i. e., an increase in the percentage of water in the serum to 0.5 per cent above its former level). Yet if during the period of observation the protein content of the blood had remained constant except for blood dilution caused by imbibition of water, the decrease in protein content of the serum of from 7.38 to 6.90 Gm. per hundred cubic centimeters represents a decrement of about 6.5 per cent of the original protein content.

The average weight of our 31 patients was 125 pounds (about 57 Kg.), and therefore the mean oral fluid intake in this experiment was 35 cc. per kilogram of

6. Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Protein Content, Plasma Specific Gravity and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

7. Heller, H., and Smirk, F. H.: Studies Concerning the Alimentary Absorption of Water and Tissue Hydration in Relation to Diuresis, J. Physiol. **76**:283, 1932.

body weight. The weight of the blood plasma in man is ordinarily estimated as 5 per cent of the body weight. Our hypothetic average patient should possess 6.25 pounds (2.8 Kg.) of plasma having a specific gravity of 1.026. (For purposes of simplification in this speculative consideration, we are using the calculated protein values for serum interchangeably with those for plasma. Actually, the fibrinogen content of normal plasma is in the neighborhood of 0.2 to 0.4 Gm. per hundred cubic centimeters, as compared with a total protein content of 7 Gm. per hundred cubic centimeters.) This is equivalent to about 2,770 cc. of plasma with a total protein content of 7.38 Gm. per hundred cubic centimeters. If all of this plasma were contained in a large glass vessel, it should require the addition of 190 cc. of water to change its protein content to 6.9 Gm. per hundred cubic centimeters.

These figures with respect to fluid intake per kilogram of body weight and decrease in specific gravity after drinking water represent the mean values in our experiment. An exception is case 31, that of W. R., 14 years old. The 2,000 cc. of water which he drank corresponded to about 1.6 times the fluid intake of our hypothetic average subject. This boy had an estimated initial plasma volume of 1,680 cc., with a protein concentration of 7.73 Gm. per hundred cubic centimeters. The decrease in protein content to 6.59 Gm. per hundred cubic centimeters after ingestion of water could have been produced by the addition of about 260 cc. of water if the plasma behaved as if it were contained in a large, distensible, impermeable receptacle.

The most extreme change in this series of 31 patients from the standpoint of water that would have been taken into the blood stream (if the protein remained within the distensible container of blood vessels and diminished in concentration solely through the addition of ingested water to plasma) occurred in case 22, that of E. J., 17 years old and weighing 146 pounds (66.2 Kg.). The amount of water ingested was 86 per cent of the mean volume intake per kilogram for the series. Yet the protein content of the plasma diminished from 6.9 to 5.77 Gm. per hundred cubic centimeters after ingestion of water. To effect this change, on the basis of our oversimplified comparison with the expected behavior of plasma in vitro, about 650 cc. of water would have had to be added to his estimated initial volume of plasma. Incidentally, this case provided the greatest decrease of any in the series in (calculated) protein content after drinking water: an absolute decrease of 1.17 Gm. per hundred cubic centimeters, or a decrement amounting to almost 16.9 per cent of the original concentration of total protein in the plasma.

The specific gravity of normal blood plasma (which is nearly that of serum) is usually considered to range from 1.0254 to 1.0288, with a mean of 1.0270 (Moore and Van Slyke [6]), but these values are based on pyknometric determinations on the blood of only 8 normal men. With respect to actual total protein content of the plasma, Salvesen [8] found values ranging from 6.34 to 7.96 Gm. per hundred cubic centimeters, with an average of 7.01 Gm. per hundred cubic centimeters for 16 normal men and 16 normal women. Recalling that the protein content of the serum is slightly less than that of the plasma and taking 6.0 Gm. per hundred cubic centimeters of protein (specific gravity of serum, 1.0250) as the somewhat arbitrary lower limit of serum protein

8. Salvesen, H. A.: Plasma Proteins in Normal Individuals, Acta med. Scandinav. **65**:147, 1926.

concentration, one notes that the initial values for specific gravity of the serum for our first 8 patients are indicative of a state of hypoproteinemia.

The problem whether the degree of diminution of specific gravity found in these experiments represents an unusual or a relatively pathologic dilution of the blood can be approached by comparison with normal variations in the specific gravity of the blood. The literature with respect to repeated determinations of the specific gravity of the blood or serum made on the same subject from hour to hour and from day to day is meager. Moore and Stewart [9] reported that in 1 subject the specific gravity of the plasma varied by 0.0007 during the course of a day. Incidentally, these investigators found a variation of not more than 0.0003 from the initial value in the specific gravity of a normal subject's plasma after imbibition of 1,000 cc. of water. Leake, Kohl and Stebbins [10] stated that there is a daily swing of 0.0033 in the specific gravity of the whole blood, the blood being more concentrated in the morning.

It has been known for years that only apparently slight changes in the concentration of the blood occur after oral intake of water in amounts comparable to those drunk by most persons under the ordinary conditions of civilized life in temperate climates. Haldane and Priestley [11] and Adolph [11a] found that the hemoglobin of the blood remains practically constant during water diuresis. Priestley [12] found that after a normal human subject had imbibed 2 liters of water the blood taken at a maximum point or diuresis showed an increase in water content (determined by loss of weight after desiccation) of from 77.44 to 77.93 per cent, or 0.63 per cent of the original value. Comparably, in the rabbit, Brahn and Bielschowsky [13] found that water given by stomach tube, in an amount equivalent to 2,000 cc. for a 70 Kg. man, produced an increase in water content of the blood of not more than 1.5 per cent above the basal level (e. g., from 81.6 to 83.1 per cent). Adler [14]

9. Moore, N. S., and Stewart, H. J.: The Variations of the Specific Gravity of the Plasma of the Blood and the Means Available for Altering It, J. Clin. Investigation **9**:423, 1930.

10. Leake, C. D.; Kohl, M., and Stebbins, G.: Diurnal Variations in the Blood Specific Gravity and Erythrocyte Count in Healthy Human Adults, Am. J. Physiol. **81**:493, 1927.

11. Haldane, J. S., and Priestley, J. G.: The Regulation of Excretion of Water by the Kidneys, J. Physiol. **50**:296, 1916.

11a. Adolph, E. F.: The Regulation of the Water Content of the Human Organism, J. Physiol. **55**:114, 1921.

12. Priestley, J. G.: The Regulation of the Excretion of Water by the Kidneys, J. Physiol. **55**:305, 1921.

13. Brahn, B., and Bielschowsky, F.: Ueber Änderung des Wassergehaltes des Blutes nach peroralen Wassergaben, Klin. Wchnschr. **7**:2004, 1928.

14. Adler, A.: Der Einfluss der Leber auf die Wasserausscheidung, Klin. Wchnschr. **2**:1918, 1923.

found in 2 normal subjects an increase in the water content of the blood of 0.35 and 2.8 per cent, respectively, of the original values after an oral intake of 1,500 cc. of water. Ziskind and associates [15] were unable to find any change in the concentration of the blood, as determined by weighing samples of dried blood, after their subjects had drunk from 1,000 to 2,500 cc. of water, although the water content was increased from 1.0 to 2.8 per cent after ingestion of 7,000 cc. in three and a half hours.

It appears therefore that the average change in water content of the blood after fairly copious ingestion of water in normal subjects is of the same general order of magnitude as that occurring in the epileptic patients in our series, if one accepts the inference that a given percentage reduction in the protein content of the serum must be compensated for by an equivalent percentage increase in the water content. When viewed from the standpoint of change in the original concentration of the diluent or solvent (water), say from 77.4 to 77.9 per cent, the increase appears negligible; yet when considered with respect to the principal solute (protein), the change looms as not inconsiderable.

When the average magnitude of decrease in protein after ingestion of water in our cases is examined in the light of the values prevailing in cases of clinical hypoproteinemia and edema, it does not appear to be clinically significant. The most instructive clinical instances of hypoproteinemia probably are furnished by the disease usually designated as nephrosis. In cases of chronic nephrosis, the critical point below which edema may occur corresponds to an albumin content of the plasma of 2.5 Gm. per hundred cubic centimeters, a total protein content of 5.5 Gm. per hundred cubic centimeters and a plasma specific gravity of 1.023.[16] In these cases a disproportionate loss of albumin (as compared with globulin) from the blood increases the predisposition to edema. Convulsions are not described as part of the clinical picture in frank cases of nephrosis marked by considerable and prolonged edema, hypoproteinemia and presumed blood hydration.[17] States of cardiac edema are not good indexes of hydremia or hypoproteinemia because there is no definite relation between edema or water balance and the protein content of the plasma in these cases.[18]

15. Ziskind, E.; Somerfeld-Ziskind, E., and Bolton, R.: Hydration Studies in Epilepsy, J. Nerv. & Ment. Dis. **89**:52, 1939.

16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 673.

17. Fishberg, A. M.: The Nephroses: II. Chronic Nephrosis, in Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, chap. 15.

18. Peters and Van Slyke,[16] p. 690.

CONCLUSIONS

In a series of 31 epileptic patients the oral administration of 2,000 cc. of water within a period of fifteen to thirty minutes combined with injections of pitressin produced a maximum average decrease in the in the specific gravity of the blood serum of 0.0014 one hour after drinking of water was begun.

In another series of 10 epileptic patients, the maximum mean decrease in specific gravity of the whole blood after ingestion of 2,000 cc. of water, without the use of solution of posterior pituitary, was 0.0011, which was statistically without significance.

By means of determination of the specific gravity it is therefore possible to detect a small change in the direction of dilution of the blood after rapid oral ingestion of 2,000 cc. of water, but this change on the average is apparently slight, corresponding to lowering of the protein content of the serum through a range of 0.5 Gm. per hundred cubic centimeters.

Only 1 of the 41 patients exhibited a convulsive seizure during the course of these tests.

It is difficult to induce a state hydremia in a clinical sense in the adult human subject by excessive oral fluid intake supplemented by antidiuretic measures.

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59 East Madison Street.

NEUROPATHOLOGIC CHANGES IN ARTERIOSCLEROTIC PSYCHOSES AND THEIR PSYCHIATRIC SIGNIFICANCE

DAVID ROTHSCHILD, M.D.
FOXBOROUGH, MASS.

Among the mental disorders associated with obvious structural damage to the brain, psychoses with cerebral arteriosclerosis occupy a prominent position. Yet there have been few recent neuropathologic studies devoted primarily to this group. Valuable information has been contributed on pathogenic aspects of cerebral vascular disease; with respect to the psychosis itself little has been added to the observations reported by Alzheimer [1] in 1902. This indicates a certain degree of stagnation in histopathologic research on the subject. One may wonder whether neuropathologic work on psychoses has attained the limits of its usefulness. Perhaps new technical developments are necessary before further progress can be made. However, it is probable that the well established histologic technics, if properly utilized, can still provide much useful information. Wertham and Wertham [2] pointed out that what is needed is a new outlook rather than new procedures. In their opinion, an impasse has been reached by adhering to the traditional methods of approach, whereby attention is concentrated almost exclusively on a minute examination of the brain and every change is regarded with the preconceived idea that it must have some specific significance. According to these authors, the field of cerebral arteriosclerosis contains contradictions everywhere; they referred especially to a lack of correlation between cerebral lesions and mental disturbances, and they suggested that the whole subject needs reconsideration from a more biologically oriented point of view.

In the past the anatomic changes have frequently been studied with little or no regard for the associated clinical phenomena, and scant attention has been given to quantitative aspects of the damage. Most writers who investigated large groups of cases did not hesitate to include those in which the vascular disease was a terminal addition to an earlier,

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From the Foxborough State Hospital.

1. Alzheimer, A.: Die Seelenstörungen auf arteriosklerotischer Grundlage, Allg. Ztschr. f. Psychiat. **59**:695, 1902.

2. Wertham, Frederic, and Wertham, Florence: The Brain as an Organ, New York, The Macmillan Company, 1934.

long-standing psychosis. Obviously, a reliable appraisal of the psychologic effects of cerebral lesions will be difficult, if not impossible, in persons whose psychologic reactions are already seriously impaired. It is generally recognized that different persons may vary in their mental reactions to similar neuropathologic alterations; yet no attempt has been made to evaluate the changes in the light of such differences.

The neglect of these aspects of the problem illustrates the uncritical and narrow outlook that tends to prevail in research on arteriosclerotic psychoses. This attitude is, no doubt, traceable to traditional acceptance of the belief that structural damage to the brain is the only factor of importance. That such a belief may require modification is suggested by earlier studies of senile psychoses.[3] When the anatomic changes were scrutinized without preconceived ideas as to their significance, it became evident that they were but one element in the total picture and that factors of a more personal nature were of etiologic importance in certain cases.

In view of the foregoing observations, it seems desirable to reexamine the neuropathologic features of arteriosclerotic psychoses with certain questions in mind. Does the relationship between anatomic and mental disturbances present common and pronounced inconsistencies which cannot be explained by demonstrable anatomic factors? Does the setting in which the lesions occur provide clues to a solution of the problem? Neubürger [4] studied the physical setting and as a result classified arteriosclerotic psychoses into hypertensive and senile types; the former was noted chiefly in relatively young persons with cardiac hypertrophy and hypertension and the latter in older patients who displayed a senile appearance, usually without hypertensive phenomena. But attention should also be directed to the psychologic setting. In this connection one may recall the work of Lewis [5] and Freeman [6] indicating that hyperplastic somatic alterations were associated with certain types of psychologic reaction. It will be shown that the somatic features described by Neubürger [4] have psychologic parallels which point to the mental makeup as a significant factor. When this is taken into account, the observa-

3. Rothschild, D.: Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**:757 (Jan.) 1937. Rothschild, D., and Sharp, M. L.: The Origin of Senile Psychoses: Neuropathologic Factors and Factors of a More Personal Nature, Dis. Nerv. System **2**:49 (Feb.) 1941.

4. Neubürger, K.: Beiträge zur Histologie, Pathogenese und Einteilung der arteriosklerotischen Hirnerkrankung, in Veröffentlichungen aus der Kriegs- und Konstitutionspathologie, Jena, Gustav Fischer, 1930-1931, vol. 6, no. 3.

5. Lewis, N. D. C.: The Pathology of Manic-Depressive Psychosis, A. Research Nerv. & Ment. Dis., Proc. **11**:340, 1930.

6. Freeman, W.: Biometrical Studies in Psychiatry: Tuberculosis, Syphilis and Cancer, Human Biol. **4**:208 (May) 1932.

tions that seem contradictory can be explained and a broader conception of arteriosclerotic psychoses arises in which consideration is given to personal, as well as impersonal, factors.

MATERIAL

Twenty-eight cases of psychoses with cerebral arteriosclerosis[7] were studied. There were 21 men and 7 women, whose ages ranged from 48 to 86 years at the time of death. Cases in which previous psychotic disturbances had occurred were excluded. This material is probably representative of the whole group of arteriosclerotic psychoses as encountered in state hospitals for mental disease. Although anatomic changes of a senile type were observed in a considerable number of cases, they were usually mild, and from a clinical point of view the occurrence of slight senile admixtures could be suspected in only a few instances. The cerebral alterations were investigated in considerable detail; for microscopic examination chief reliance was placed on large sections stained by the Nissl method and other standard procedures.

GROSS PATHOLOGIC CHANGES

General Somatic Changes.—The most striking disturbances were observed in the cardiovascular system and the kidneys. Cardiac hypertrophy was noted in the great majority of instances. The weight of the heart was recorded in 27 cases and ranged from 235 to 670 Gm., with an average of 415 Gm. The value was below 300 Gm. in 4 cases and above 400 Gm. in 17 cases. Moderate valvular thickening was present in 2 cases and severe thickening and contraction in a similar number. Coronary sclerosis was noted in 25 cases and aortic sclerosis in 27 cases of the group, pronounced changes usually being observed. This is contrary to Neubürger's[4] statement that severe generalized arteriosclerosis seldom occurs in patients with arteriosclerotic psychoses. The kidneys showed arteriosclerotic infarcts in 10 cases and chronic progressive vascular nephritis in 5 cases. Carcinomatous growths were not encountered, thus confirming Neubürger's[4] observation that such tumors are rare in patients with cerebral arteriosclerosis.

Gross Neuropathologic Changes.—Atherosclerotic changes of the cerebral arteries were observed in all but 1 case, and as a rule the alterations were severe. Areas of softening occurred in 25 cases and recent hemorrhages in 6 cases. Single focal lesions were encountered in 6 cases and two or more in the others. In 10 cases the foci were large. In 1 instance gross lesions were not noted, and in another the brain presented only a few tiny foci in the basal ganglia. The cortex

7. In accordance with general usage, the term arteriosclerosis is used in a broad sense to include atherosclerosis, which affects the larger arteries, arteriolosclerosis and capillary or arteriocapillary fibrosis. These changes have been described in textbooks of neuropathology and elsewhere and do not require discussion here.

and the white matter of the cerebral hemispheres were involved in 20 cases, in 8 of which changes were not present elsewhere. The temporo-occipital regions were affected with greatest frequency. In 18 cases lesions were present in the basal ganglia, the damage being confined to these structures in 5 cases. The putamen was especially susceptible, often exhibiting a number of small cystlike losses of substance, a status lacunaris. The alterations commonly predominated on one side or the other, but in the group as a whole the two sides were equally vulnerable. The cerebellum was involved in 5 cases and the midbrain and pons in 1 case. Pachymeningitis haemorrhagica interna was noted in 1 case. The weights of the brain, which were available in 27 cases, ranged from 975 to 1,510 Gm., the average being 1,280 Gm.

MICROSCOPIC CHANGES

Vascular and Meningeal Changes.—The pia-arachnoid exhibited minor alterations except for reactive disturbances near destructive cerebral lesions. The atherosclerotic changes mentioned in the preceding section were most frequent in the larger vessels at the base of the brain and were relatively uncommon in vessels of medium size. Narrowing of the lumens was often considerable, but complete closure was observed in only 1 brain.[8] Calcification of the media was not encountered.

The small meningeal vessels regularly presented involvement, which was severe and widespread in many cases. In general, the alterations were of the type described as arteriolosclerosis, the vessels showing thickening of their walls, with frequent hyaline changes and swelling of the endothelial cells (fig. 4). Similar lesions were observed in the choroid plexus, parts of which were available in 26 cases. The choroidal tufts exhibited an increase of connective tissue and often contained calcareous deposits. In several cases the cells of the villi seemed atrophied.

The cortical vessels were altered in all cases, severe or moderately severe damage being noted in 21. The commonest type of change consisted of adventitial thickening and proliferation, sometimes combined with endothelial swelling. The precapillaries were chiefly affected. In many instances the lesions corresponded to descriptions of arteriocapillary fibrosis. Hyaline changes were encountered in few cases. While the lumens of the vessels were often decreased, complete closure was rarely observed. Many of the veins were congested. Elsewhere in the brain similar disturbances were noted, but hyaline degeneration and dilatation of the perivascular spaces occurred frequently in the white matter and the basal ganglia, the latter usually showing greater vascular involve-

8. Since serial sections were not cut, it is possible that complete closure occurred more frequently than was demonstrated in this study.

ment than any other region. In most cases the vessel walls of the globus pallidus had moderate amounts of calcareous material. Four brains displayed rare aneurysmal dilatations of intracerebral vessels.

Changes in Cerebral Cortex and White Matter.—Various types of focal lesion were observed in every case. Perivascular loss of cellular elements with increase of glia fibrils, conforming to Alzheimer's perivascular gliosis, was noted in all the brains (fig. 1). These lesions were not abundant; they occurred chiefly in the cortex.

Acellular or devastated areas (Alzheimer's senile cortical devastation, or *Verödungen*) were observed in the cerebral cortex in 21 cases, being abundant in 6 cases. They were characterized by more or less complete disappearance of nerve cells, without dissolution of the nerve substance or noteworthy reactive phenomena (fig. 2). They varied greatly in shape and size but were seldom large enough to occupy a whole low power field. In some instances they were located in clusters within two or three adjacent convolutions, suggesting an origin based on involvement of one large vessel.

Cortical areas of softening or scars resulting therefrom were noted in 18 cases, in 5 of which the alterations were abundant (fig. 3). In 9 cases of this group and in one additional instance similar lesions were present in the white matter (fig. 2). Small areas occasionally displayed a spongy state, but extensive damage of this type did not occur.

Small cortical hemorrhages of old or recent origin (fig. 4) were encountered in 10 cases, in 4 of which similar changes were seen in the white matter. In most instances the lesions were not numerous. Acellular areas or foci of softening or both occurred in all but 1 of these cases.

Pale areas (*Erbleichungen*) were noted in 5 cases, but they were not common enough to be considered an important feature. État vermoulu and verrucous atrophy, which have been described by some authors in arteriosclerotic brains, were not observed.

Most of the brains with acellular areas also showed foci of softening, the former occurring without the latter in 6 cases. Furthermore, the two types of lesion were often immediately adjacent, with one merging into the other, especially near the periphery of areas of softening (figs. 2 and 3). As a rule, the damage was most pronounced in the occipital lobe and the posterior parts of the parietal and temporal lobes. A noteworthy difference in the susceptibility of the different cortical layers could not be detected. Foci occasionally extended along one or more layers for short distances (fig. 3), but widespread laminary involvement was not encountered. In 5 cases Sommer's sector of the cornu ammonis was completely or almost completely destroyed (fig. 2), and in 9 cases it exhibited smaller focal lesions.

Spielmeyer's myelin sheath stain, which was used in 17 cases, disclosed irregular and poorly defined areas of demyelination (fig. 5). They usually occupied one or several low power fields, but smaller patches were not uncommon; most of them failed to show pronounced reactive phenomena or lipoid deposits. All variations from slight to complete demyelination occurred. The lesions were observed singly

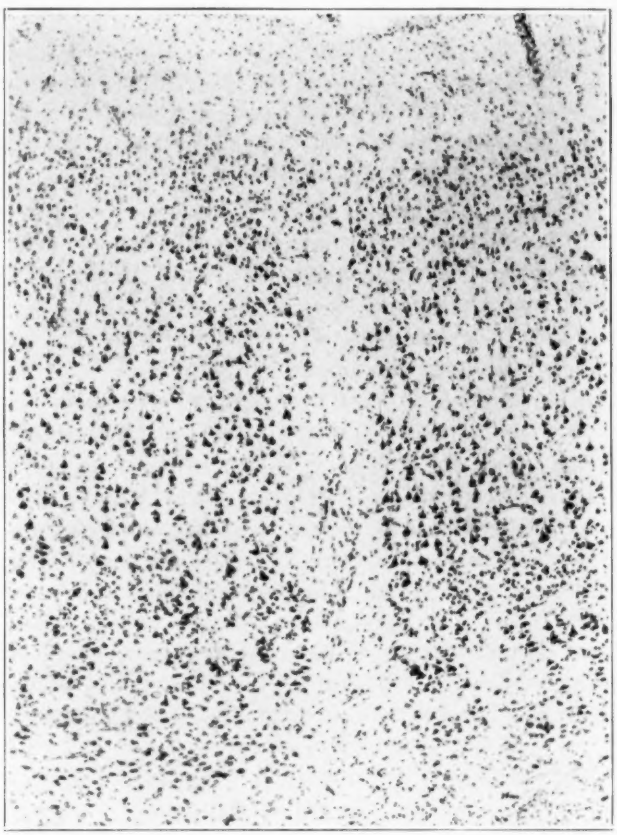

Fig. 1.—Section from the cerebral cortex, illustrating a focal lesion corresponding to Alzheimer's perivascular gliosis. There is perivascular loss of cellular elements, usually associated with a perivascular increase of glia fibers. Thionine stain; × 65.

at widely scattered points deep in the white matter. Although they did not involve extensive areas, they were a prominent feature in 3 cases. The Bielschowsky stain revealed a decrease in the number of axis-cylinders in the affected areas; this usually seemed less extensive than the loss of myelin sheaths.

Apart from the focal disturbances, striking parenchymal changes did not as a rule occur. Diffuse cerebral atrophy was not uncommon but was seldom pronounced. In general, the nerve cells as observed in the Nissl stain were well preserved, and the cytoarchitecture was not obvi-

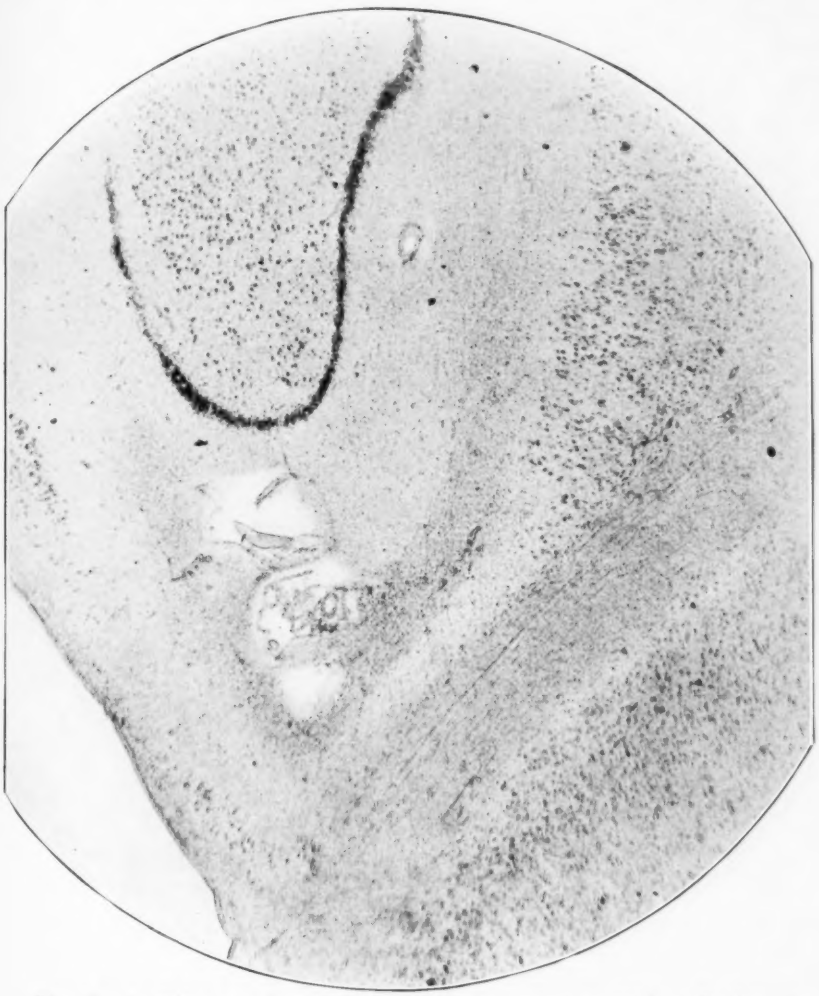

Fig. 2.—Acellular or devastated area in the cornu ammonis, affecting the nerve cell band as it swings down from the hippocampal gyrus on the right and bends sharply upward to the left. The lesion consists of a focal loss of nerve cells without disintegration of the tissues or noteworthy reactive phenomena. The adjacent white matter above this lesion shows a small area of softening, with complete disintegration of the tissues to form cystlike spaces. Thionine stain; × 26.

ously disturbed. However, the scarlet red stain disclosed considerable lipoid accumulations in many of the cells and in the walls of some blood

vessels. Marginal gliosis, perivascular neuroglial proliferation and a diffuse increase of astrocytes in the white matter were occasionally noted. In most cases considerable numbers of corpora amylacea were encountered. The Turnbull blue method revealed a slight or moderate

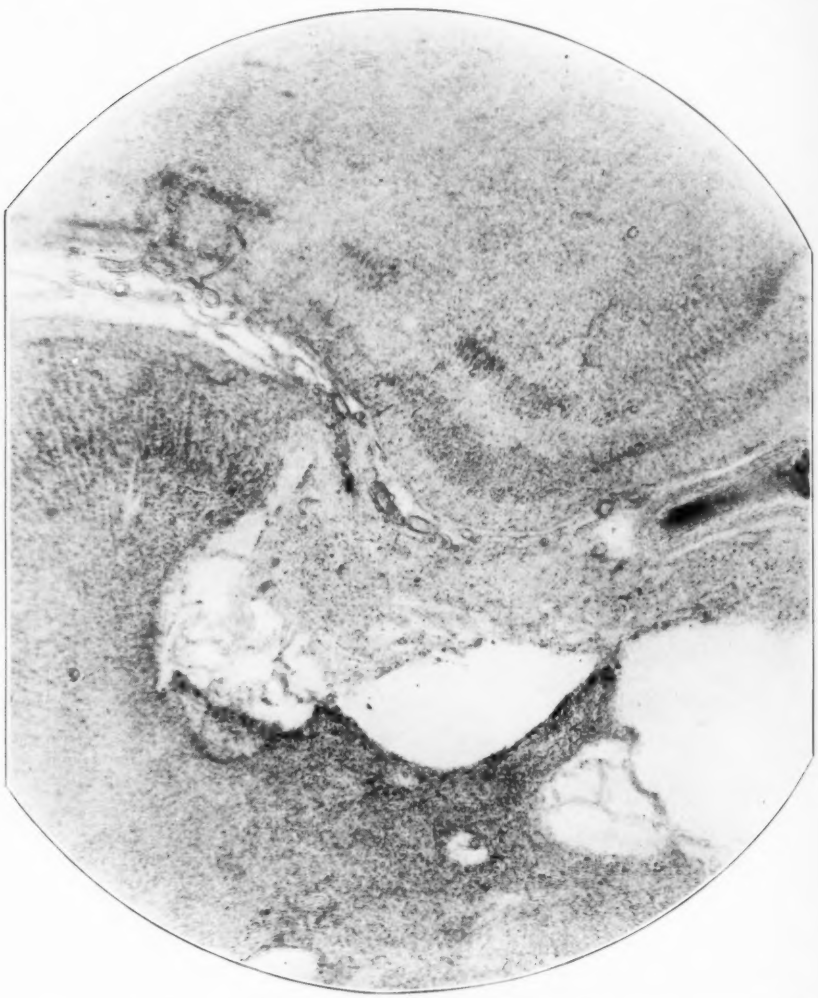

Fig. 3.—Section from the cerebral cortex, showing in the lower convolution a recent area of softening with complete disintegration of the tissues and in the upper convolution an area of incomplete destruction, which in places leaves intact the second, the upper part of the third and the fourth layer. Thionine stain; × 26.

increase of iron in 9 cases; the iron occurred in widely scattered neuroglia cells of all types, in the walls of small blood vessels and, less frequently, in the form of slight diffuse staining of the white matter.

Complicating Senile Changes.—Senile plaques were observed in 14 brains, 6 of which showed only a scanty number of lesions. One brain exhibited a great abundance of plaques. Neurofibrillar changes of the Alzheimer type were seen in 8 brains, 5 of which also displayed plaques. In all instances the neurofibrillar lesions were confined to the cornu ammonis or to the neighboring parts of the hippocampal gyrus.

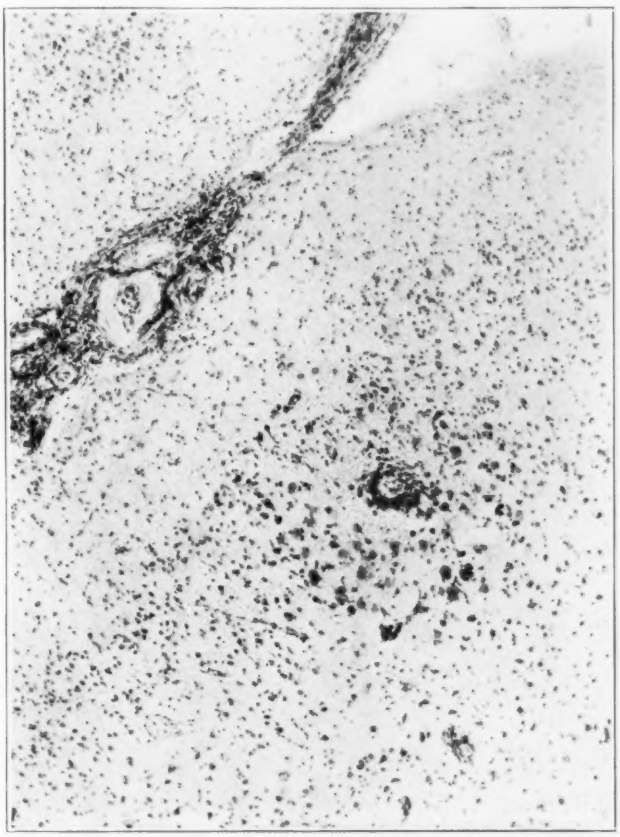

Fig. 4.—Section showing the remains of an old small hemorrhage in the cerebral cortex. There is blood pigment in the adventitial spaces of a thickened vessel and in the surrounding nerve tissue with perivascular proliferation of large neuroglia cells. Some of the pigment lies free in the tissues, and some is contained in cellular elements. Above and to the left of this focal lesion, two small meningeal vessels show severe hyaline changes. Thionine stain; × 65.

Alterations in Other Parts of the Brain.—As a rule the basal ganglia showed more pronounced changes than other parts of the brain, though the damage to this region completely dominated the picture in only 2 cases. Focal lesions, chiefly areas of softening or scars resulting there-

from, were noted in 24 cases. The perivascular spaces were dilated, and the surrounding nerve tissue was often rarefied and largely devoid of cells. In some instances the process was extensive enough to be

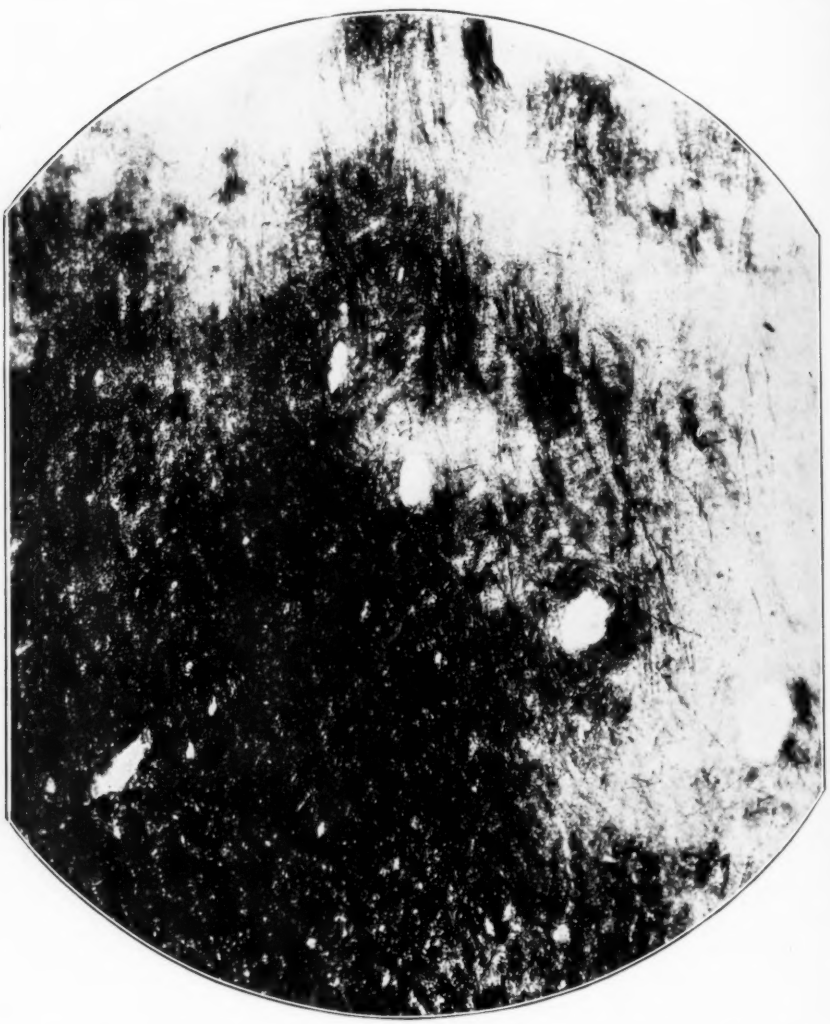

Fig. 5.—Section from the white matter, showing the ragged margin of an irregular area of demyelination, without disintegration of the tissues or noteworthy reactive phenomena. This conforms to the type of lesion described in Binswanger's subcortical encephalitis. Spielmeyer's myelin sheath stain; × 52.

termed status cribratus (fig. 6). Small cystlike losses of tissue, constituting a status lacunaris, were commonly observed. The putamen generally displayed the greatest involvement; here the nerve cells not

infrequently appeared diffusely diminished in number. The cells of the thalamus usually contained lipoid accumulations. In most cases considerable amounts of iron were present in the putamen, pallidum and substantia nigra.

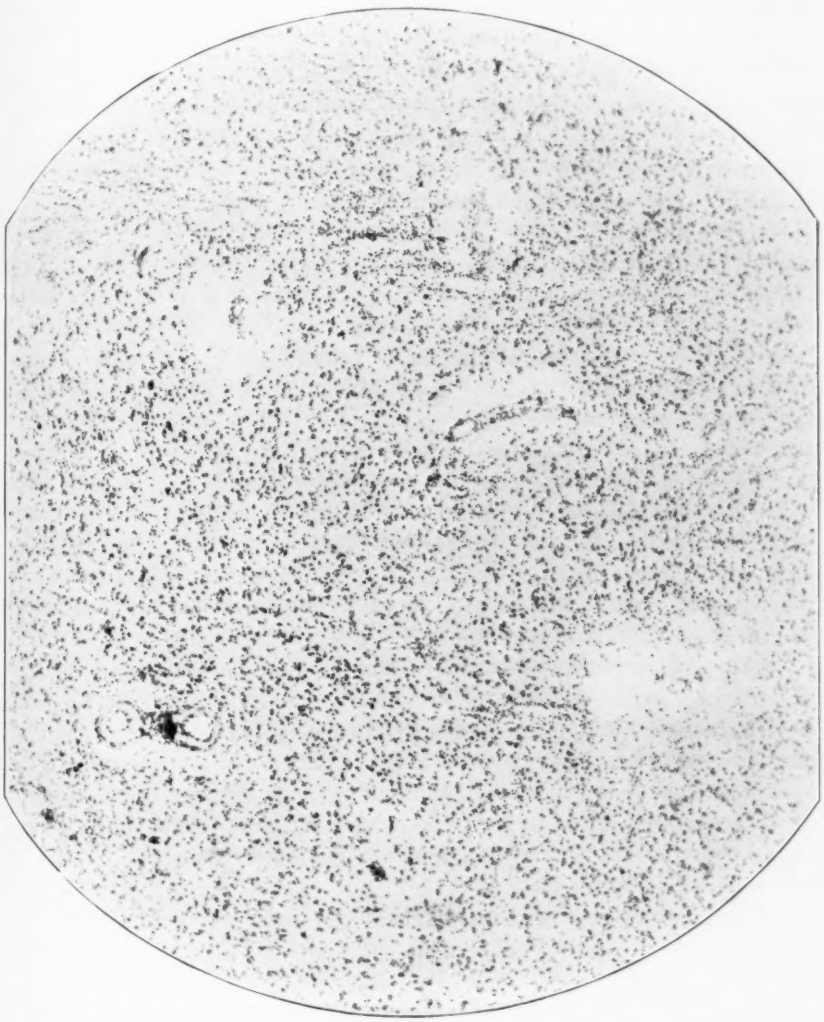

Fig. 6.—Section from the putamen in a case of parkinsonism. The perivascular spaces are dilated and the surrounding nerve tissue is rarefied, presenting status cribratus. The nerve cells, especially the large ones, are diminished in number. Two small vessels in the lower left portion of the figure exhibit hyaline degeneration. Thionine stain; × 52.

A detailed study of the brain stem was not made, but in 4 cases a few small areas of softening were observed in the pons. The cere-

bellum showed small focal lesions in 16 cases. The commonest types of change were acellular areas in the granular layer and foci of softening in the white matter. As a rule, the lesions were not numerous, involvement which approached in severity that of the cerebral hemispheres being present in only 7 cases.

COMMENT ON NEUROPATHOLOGIC CHANGES

In evaluating the cerebral damage, gross observations alone may be misleading. For example, gross examination may disclose unimportant focal lesions, or even none at all, in brains which exhibit numerous areas of destruction under the microscope. On the other hand, in patients with senile dementia the brain may present gross foci, but histologic study indicates that they are minor features of the whole picture. In elderly psychotic patients of all types the basal vessels are often severely atherosclerotic and the small vessels may be considerably thickened without leading to damage of the nerve tissue. A reliable estimation of the anatomic factors can be obtained only with the aid of detailed microscopic observations.

The various types of focal lesions and their appearance at different stages of the disintegrative process will not be described, since they have been discussed in great detail by Neubürger,[4] Spielmeyer [9] and others. The most important tissue changes were areas of softening, that is anemic infarcts,[10] either large or small, and acellular areas (*Verödungen*) of microscopic size. However, all brains showed a variety of lesions, transitions sometimes occurring from one form to another.

The observations suggest that it is a factitious procedure to separate the various types of focal disturbance too sharply from each other. Acellular areas and Alzheimer's perivascular gliosis are regarded as foci of incomplete destruction, whereas areas of softening represent a complete breakdown of the nerve tissue, but all are merely expressions of differences in the severity, tempo and localization of the same pathologic process. They are not separate anatomic or clinical forms of arteriosclerotic psychosis.

This also applies to Binswanger's chronic progressive subcortical encephalitis,[11] which is traditionally regarded as a special type of arteriosclerotic psychosis. Although Binswanger [11] reported 8 cases in his original paper, published in 1894, the disease has apparently become

9. Spielmeyer, W.: Histopathologie des Nervensystems, allgemeiner Teil, Berlin, Julius Springer, 1922.

10. According to Cobb (Am. J. Psychiat. **90**:947 [March] 1934), all anemic infarcts begin as hemorrhagic infarcts. In the present study, however, small foci that seemed fresh usually failed to show hemorrhagic phenomena.

11. Binswanger, O.: Die Abgrenzung der allgemeinen progressiven Paralyse, Berl. klin. Wchnschr. **31**:1137 and 1180, 1894.

progressively rarer, and few instances have been described in recent years. It is possible that Binswanger [11] was really dealing with a heterogeneous group, since some of his cases were reminiscent of Pick's lobar atrophy and Alzheimer's disease. Slight alterations of the type observed by Binswanger [11] were often noted in the present group, but even when these lesions were more pronounced they were merely one element in a broader anatomic process. One may thus say that "traces" of Binswanger's subcortical encephalitis are frequently observed in the brains of patients with arteriosclerotic psychoses, but the pathologic picture described by him as an entity scarcely merits consideration as a separate form of the disorder.

Although the involvement may predominate to some extent in the cerebral cortex, white matter or basal ganglia, none of these structures was completely spared. Hence a classification of psychoses with cerebral arteriosclerosis based on localization of the lesions, such as that of Kodama,[12] fails to do justice to all the facts. A classification based on the size of the vessels involved, which was advocated by Rhein, Winkelman and Patten,[13] is perhaps more justifiable, since the small meningeal and intracerebral vessels occasionally showed severe changes without noteworthy alterations of the large arteries. However, both large and small vessels were usually implicated, and it was not possible to differentiate clearcut clinical forms which corresponded to the grouping proposed by these authors.

Senile plaques were observed in 50 per cent of the cases, but they were not as a rule abundant. While these lesions are intimately associated with senile dementia and Alzheimer's disease, they may also occur in the brain of any elderly person. In a previous study [3] of the brains of 50 such patients with miscellaneous nonsenile psychoses, plaques were noted in half the group. One may therefore conclude that arteriosclerotic patients are not more susceptible to such changes than older psychotic patients in general.

The pathogenesis of the lesions associated with cerebral arteriosclerosis has been discussed in detail by Cobb and Blain,[14] Neubürger,[4] Hiller [15] and others and does not require extended comment here. The present data were consistent with the generally accepted view that circumscribed damage to nerve tissue does not necessarily depend on complete

12. Kodama, M.: Die regionäre Verteilung der arteriosklerotischen Veränderungen im Grosshirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:597, 1926.

13. Rhein, J. H. W.; Winkelman, N. W., and Patten, C. A.: Mental Conditions in the Aged, Arch. Neurol. & Psychiat. **20**:329 (Aug.) 1928.

14. Cobb, S., and Blain, D.: Arteriosclerosis of the Brain and Spinal Cord, in Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933.

15. Hiller, F.: Zirkulationsstörungen im Gehirn, eine klinische und pathologisch-anatomische Studie, Arch. f. Psychiat. **103**:1, 1935.

or permanent closure of blood vessels. Since the work of Spielmeyer,[16] such damage has often been attributed to vasomotor disturbances, but clearcut evidence in favor of this idea cannot well be obtained in a disorder which shows widespread structural alterations of the blood vessels. The observations suggested that impairment of cardiac function contributed to the development of focal lesions in some cases by causing general weakening of the blood flow. Thus, in 12 cases outspoken attacks of cardiac dysfunction were displayed [17] at one time or another during the course of the illness. The importance of this factor has been mentioned by Wertham and Wertham [2] but has not been sufficiently emphasized elsewhere in the literature.

CLINICAL CONSIDERATIONS

At this point only a few clinical phenomena that are pertinent to the present study are mentioned; the relation between mental and anatomic changes will be discussed later. One of the characteristic features of the group was represented by attacks of confusion or delirium-like episodes. Equally characteristic was a tendency for periods of improvement to occur whenever the psychosis was of any considerable duration. At the same time, a certain degree of permanent intellectual impairment usually remained; this was as a rule slight or moderate in the beginning, but tended to increase. Abnormal emotional reactions were prominent in 10 cases. They seemed for the most part impersonal, and in general there was a scarcity of more complex psychologic disturbances. Thus, instances of well developed paranoid or manic pictures were not encountered. In view of the size of the group, their absence may perhaps be accidental, though Alzheimer [1] remarked that he had never observed grandiose or elated states in patients with arteriosclerotic psychoses.

In many cases unstable and asocial prepsychotic traits of personality were noted. For example, 1 patient was depicted as a bad-tempered, domineering man who had always been a tyrant. A patient who had been excessively alcoholic at an earlier age was described as tense and inclined to be depressed. Another had been miserly, irritable, self centered and unsociable. Another was regarded as peculiar all his life, lacking in ambition, constantly wanting attention and failing to support his family. One patient had been odd, seclusive and retiring and had led a lonely life. Another was described as a disagreeable, vindictive

16. Spielmeyer, W.: Vasomotorisch trophische Veränderungen bei zerebraler Arteriosklerose, Monatschr. f. Psychiat. u. Neurol. **68**:605, 1928.

17. It might be argued that such cases should be diagnosed as instances of psychosis due to cardiac disease rather than of arteriosclerotic psychosis, but from a neuropathologic viewpoint they did not differ from the other cases and most of them were typical clinically.

and untruthful woman who had frequently been subject to temper tantrums. Additional examples could be given but these should suffice as brief illustrations of the material encountered.

SIGNIFICANCE OF THE NEUROPATHOLOGIC CHANGES

Since the work of Alzheimer,[1] it has generally been taken for granted that the cerebral changes associated with arteriosclerotic psychoses wholly explain the occurrence of the mental disorder. This belief has rarely been subjected to critical examination, in spite of certain serious objections to its complete validity. As pointed out by Wertham and Wertham,[2] no account has been taken of the fact that cerebral arteriosclerosis is often noted in patients who fail to show psychotic disturbances. It might be thought that quantitative differences play a decisive role, but concrete evidence in favor of this idea has not been forthcoming. On the contrary, the available information tends to suggest that simple quantitative factors alone cannot be held responsible for the presence or absence of a psychosis. According to Wertham and Wertham,[2] the same lesions which are noted in patients with arteriosclerotic dementia may occur in patients without any dementia. Unfortunately, the frequency of such an occurrence is not known, and it was not possible to include control material from mentally normal persons in this investigation.[18] However, from a study of the present group, the following statements may be made.

In only a few cases were the cerebral changes so widespread that one might be inclined to stress the quantitative factor; in many instances the alterations were not extensive. There was no consistent correlation between the severity of the mental changes and the extent of the anatomic involvement. For example, the structural damage observed in patients with severe intellectual impairment was sometimes less pronounced than that observed in patients with much milder mental symptoms. These discrepancies occurred too frequently and were too striking in certain cases to be dismissed as unimportant. They could not be accounted for by differences in the localization of the process or the type of involvement.[19] Thus, a scrutiny of the data without preconceived ideas indicates that even the impersonal aspects of the psychosis cannot be adequately explained by anatomic considerations alone.

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18. Elderly patients with manic-depressive or schizophrenic psychoses often showed cerebral vascular changes which were as extensive as those observed in the group with arteriosclerosis, but reliable clinical correlations could not be established.

19. There was nothing in the observations to support the view of Alford (Am. J. Psychiat. **94**:615 [Nov.] 1937) that "intellectual defect per se is not produced by lesions other than those of the central portion of the left hemisphere in right-handed persons."

In an earlier study of senile dementia [3] the same deadlock occurred in attempting to explain the psychosis on an anatomic basis. A solution of the problem was provided by turning from the neuropathologic disturbances to the patients, with the object of determining how different persons try to cope with such disturbances. It was pointed out that visceral organs are able, within certain limits, to compensate for damage to their structure, and it seemed reasonable to believe that such an important organ as the brain possesses similar potentialities. Lewis [5] and Freeman [6] showed that compensatory reactions in somatic and psychologic fields go hand in hand. For example, patients with paranoid or affective psychoses tend to resist deterioration or to get well, and in their somatic reactions they display a strong capacity for the development of cardiac hypertrophy or other lesions indicative of compensatory tissue processes. Somatic changes of this type were usually lacking in patients with a disorder such as dementia praecox, which is noncompensatory at the psychologic level in the sense that the patients usually succumb to the stresses that bring about the psychosis and deteriorate.

In the senile group [3] the patients with strong hyperplastic cardiovascular alterations showed relatively little deterioration, despite severe cerebral changes. It was therefore suggested that the discrepancies between neuropathologic and clinical features were based on differences in the capacity of different persons to compensate for structural damage to the brain. Depending on this capacity, some persons were able to compensate for cerebral changes so well that mental abnormalities failed to occur, whereas others broke down completely in the face of similar, or even less severe, alterations.

The validity of this interpretation for the arteriosclerotic patients is indicated by a comparison of their somatic reactions and their ability to compensate for neuropathologic involvement. The pertinent data are presented in the table, which contains quantitative estimations of cerebral damage and permanent intellectual deterioration in each case,[20] the cardiac weight serving as a measure of the compensatory capacity of the cardiovascular system. It is realized that these estimations are only approximations; yet they disclose certain relationships which seem fairly consistent.

Thus, patients with mild or moderate intellectual deterioration often presented extensive cerebral changes, suggesting that their compensatory capacity in psychologic fields was strong; such patients usually showed marked cardiac hypertrophy as an indication of strong compensatory cardiovascular processes. Outspoken examples may be noted in cases

20. The cases in which the psychosis consisted solely of rapidly fatal confused states are omitted from the table; in such cases one could not well speak of permanent mental deterioration, nor could quantitative differences in the acute confused states be noted.

5 and 13 in the table. These cases fall under Neubürger's [4] hypertonic type of arteriosclerotic psychosis. On the other hand, in a smaller number of cases (4, 14, 15, 17 and 21 in the table) the powers of resistance were weaker, severe mental deterioration being exhibited despite relatively mild cerebral alterations, and, on the somatic side, cardiovascular compensatory changes were absent. Although corresponding to Neubürger's [4] senile type of arteriosclerotic psychosis, this form was not confined to the older patients. Furthermore, his hypertonic type

Comparison of the Amount of Cerebral Damage, Degree of Permanent Intellectual Deterioration and Cardiac Weight in Twenty-Three Cases of Arteriosclerotic Psychosis

Case No.	Age at Death	Cardiac Weight, Gm.	Cerebral Damage *	Intellectual Deterioration *
1	48	435	3	2
2	49	540	4	3
3	55	440	2	1
4	58	335	1	4
5	63	540	4	1
6	63	350	2	2
7	65	450	2	1
8	68	425	2	1
9	72	375	3	2
10	73	445	3	2
11	74	360	2	2
12	75	440	2	1
13	76	670	4	2
14	76	245	2	3
15	77	250	2	3
16	77	475	3	2
17	78	235	1	3
18	79	355	2	2
19	79	305	4	3
20	79	465	4	3
21	79	255	2	3
22	80	.....	2	2
23	86	425	3	2

* The amount of cerebral involvement and degree of intellectual impairment are represented by numbers; slight changes are indicated by 1, and moderate, severe and very severe changes by 2, 3 and 4, respectively.

affects patients of all ages. Neubürger's [4] types can more adequately be called forms with strong and weak compensatory reactions, with the recognition that all gradations occur between the two extremes. One may thereby describe the disorder in terms which indicate that the qualities of the living patient are factors in the psychosis.

White [21] stressed the value of terms which are equally applicable at somatic and at psychologic levels. He pointed out that by their utilization the conflicting expressions "body" and "mind" will grow progressively less useful, and the concept of the organsim as a whole comes to function in a productive manner. The concept of compensa-

21. White, W. A.: The Social Significance of Mental Disease, Arch. Neurol. & Psychiat. **22**:873 (Nov.) 1932.

tion has the special advantage of being well known in its psychopathologic as well as its general medical applications, and it has proved helpful in understanding problems in both fields. On the somatic side, arteriosclerotic psychoses arise from decompensation of the cerebral circulation, in that an adequate flow of blood through the brain is not maintained. Sooner or later there is a breakdown of compensation on the psychologic side, represented in its more acute forms by attacks of confusion. These attacks are usually followed, unless they terminate fatally, by varying degrees of improvement, that is, by more or less successful compensatory attempts. Psychologically as well as anatomically, psychoses with cerebral arteriosclerosis may thus be regarded as expressions of decompensation at the cerebral level.[22]

In an earlier study [3] the impression was obtained that the compensatory reactions of the senile group as a whole were not strong. Thus, atrophic changes predominated in the somatic field and severe and progressive mental deterioration in the psychologic field. In contrast to this, the arteriosclerotic patients as a rule exhibited pronounced compensatory cardiac phenomena. Similarly, they showed a more vigorous compensatory capacity in psychologic fields than the senile patients, as indicated by a tendency to improvement even if only temporary, less severe mental deterioration and better preservation of the personality in general. These clinical differences between the two groups are well known. They cannot always be due to differences in the type or extent of the cerebral involvement, for some of the arteriosclerotic patients also had outspoken senile changes in the brain.

For example, in 1 case the brain showed great abundance of senile plaques; yet the patient had been normal mentally until a massive focal lesion developed, which terminated fatally in sixteen days. In another case, in which numerous senile plaques were observed, the psychosis consisted solely of a sudden attack of confusion, lasting for several days. In other words, in both cases the patients failed to display senile mental disturbances despite the presence of changes which, in such numbers, are ordinarily associated with long-standing senile dementia. Furthermore, some of the focal lesions were older ones, which had unquestionably been present before the onset of the psychosis. The patients did not break down mentally until they were overwhelmed by massive damage to the brain. In harmony with their strong capacity to resist cerebral involvement, they exhibited pronounced hyperplastic cardiac alterations.

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22. The comparison may be carried further by pointing out that many of the excessive emotional reactions can perhaps be looked on as indications of overcompensation in psychologic fields, analogous to the overcompensation frequently noted in the cardiovascular system.

These observations and others of a similar nature serve to emphasize the point that even severe cerebral lesions do not inevitably produce psychotic disturbances. It is not denied that quantitative differences may play a role, but within certain limits the factor which determines whether a psychosis is or is not going to occur may be the person's capacity to compensate for the damage rather than the damage per se. The question now arises: Are there individual factors which impair this capacity and thereby lead to the outbreak of a psychosis? From observations made on senile patients [3] the idea was expressed that difficult personal problems arising in everyday life might have such an effect, upsetting an equilibrium which had hitherto been preserved. In the present group immediate psychologic problems did not appear to play a noteworthy role, though it is possible that more intensive study of individual cases might disclose difficulties of this type. However, there was one feature which seemed significant, namely, the distinctly ill balanced personalities displayed by many of the patients. Such persons are probably more vulnerable mentally, possessing less reserve powers, and as a result psychoses are more apt to develop in them than in other persons with cerebral arteriosclerosis.

Of course, it is not claimed that influences of the foregoing type are in themselves responsible for the occurrence of arteriosclerotic psychoses. Structural damage to the brain is a constant feature and in some instances wholly accounts for the mental disorder. But in many instances the neuropathologic changes alone cannot satisfactorily explain the presence of a psychosis. In such cases the person's capacity to compensate for tissue damage and conditions which may impair this capacity are of immediate importance; the cerebral alterations merely represent a handicap which might well be overcome if other unfavorable influences did not exist. Thus, patients with an arteriosclerotic psychosis should be scrutinized not as passive carriers of a morbid structural process, but as living persons whose inherent and acquired traits and individual problems are a pertinent object of study. Instead of approaching the subject from a too one-sided anatomic point of view, one should attempt to estimate to what extent anatomic factors and to what extent broader biologic or more personal factors are concerned in each case.

SUMMARY

A neuropathologic study of 28 cases of psychoses with cerebral arteriosclerosis is reported.

In all cases there was a variety of focal cerebral lesions, the most important of which were areas of softening and acellular or devastated areas. The observations indicated that the different types of focal lesions do not constitute separate anatomic or clinical forms of arteriosclerotic

psychosis. The basal ganglia were more vulnerable than other parts of the brain, but in no case was the damage confined exclusively to these structures.

A scrutiny of the relationship between the extent of the neuropathologic changes and the degree of intellectual deterioration revealed numerous discrepancies; in many instances the psychosis could not be adequately explained by anatomic considerations alone. It is believed that the discrepancies are based on differences in the capacity of different persons to compensate for damage to the brain. Examples are given to illustrate that cerebral lesions do not inevitably produce psychotic disturbances. Attention is directed to qualities of the living patient as an important factor in the origin of the mental disorder. It is suggested that patients with an ill balanced mental makeup possess weaker compensatory powers and are thus more likely to acquire a psychosis than other persons with cerebral arteriosclerosis.

Foxborough State Hospital.

INTRANEURAL CONDITIONING

CEREBELLAR CONDITIONED REFLEXES

W. J. BROGDEN, PH.D.
AND
W. HORSLEY GANTT, M.D.
BALTIMORE

The relation of conditioned reflex function to anatomic pathways has been investigated chiefly by the method of extirpation of different parts of the central nervous system, e. g., the cerebral cortex. The function which disappears after extirpation is then assumed to depend on the part extirpated. Such early experiments led Pavlov to believe that the cerebral cortex was indispensable for the elaboration of the conditioned reflex, but this view has been challenged by the subsequent studies of Zeliony,[1] in Pavlov's own laboratory, and the work in the laboratories of Bard [2] (Bromiley) and Culler (Finch, Shurrager and Culler [3] and others). It should be mentioned in this controversy that Pavlov's conclusions were drawn from work with salivary dogs, while other investigators have used motor conditioned reflexes.

Notwithstanding the best surgical technic employed by some of these investigators, certain objections are particularly inherent in the method of extirpation. First, the gross mutilation of so fine and complex an organ as the brain is likely to have effects more widespread than simply the absence of the removed part. It is, in the words of Pavlov,[4] as if one struck a delicate machine with a sledge hammer and then studied the results. Furthermore, a three-legged stool falls when any one leg is removed, although that leg is not wholly responsible for holding up the stool—an analogy often used by Adolf Meyer.

From the Pavlovian Laboratory of the Phipps Psychiatric Clinic, Johns Hopkins University School of Medicine.

Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 11, 1941.

1. Zeliony, G. P.: Observations on Dogs with Cerebral Hemispheres Removed, Proc. Eleventh Internat. Physiol. Cong., 1923.

2. Bard, P., in Macleod, J. J. R.: Macleod's Physiology in Modern Medicine edited by P. Bard, St. Louis, C. V. Mosby Company, 1941, p. 161.

3. Shurrager, P. S., and Culler, E. A.: Conditioning in the Spinal Dog, J. Exper. Psychol. **26**:133-159, 1940.

4. Pavlov, I.: Lectures on Conditioned Reflexes, New York, International Publishers, 1928, vol. 1.

Recently other methods have been employed obviating some of the disadvantages of extirpation. First, there is the method of tracing action currents from one part of the nervous system to the other on stimulation at a distant point—a method which has been successfully employed by Dusser de Barenne and McCulloch, Bard and his associates (Marshall, Curtis, Woolsey) and others.

This method, however, is not yet applicable to the study of a function like the conditioned reflex, requiring an intact, unanesthetized animal, which can be studied over a comparatively long period rather than simply in the acute stage.

The procedures that we shall outline had for their object the successive elimination of the various parts of the conditioned and unconditioned reflex arcs while at the same time the intactness and normality of the animal were preserved.

For the purposes of orientation it is well to enumerate the elements of the ordinary conditioned reflex arc (viz., unconditioned reflex arc plus suprasegmental receptor-conditioned stimulus and central connection): unconditioned stimulus, involving external receptor, afferent nerve, and central connection; unconditioned reflex arc, involving efferent nerve and executor organ, and conditioned stimulus, involving a second receptor system plus central connection, efferent nerve and executor organ.

We have eliminated (functionally) one by one the following elements of both the conditioned and the unconditioned reflex arc, viz., beginning at the receptor periphery: external receptor organ; peripheral receptor nerve; posterior spinal ganglion, fasciculi cuneatus and gracilis, receptor tracts caudal to the area striata and some other cortical zones; all structures caudal to the cerebellum (present study); all structures caudal to the motor area of the cerebral cortex, and, beginning from the efferent side and proceeding centripetally, external executor organ and peripheral nerve.

It has proved possible to elaborate readily conditioned reflexes after having eliminated both the afferent and the efferent limb of the unconditioned reflex arc, as well as the superimposed afferent limb of the conditioned reflex arc. However, as concerns the unconditioned reflex, the process of short circuiting cannot be carried as far forward as the motor area of the cerebral cortex.

In order to accomplish this short circuiting the usual conditioned or unconditioned stimulus was applied somewhere inside the periphery or within the central nervous system itself. Such conditioning, which occurs entirely within the central nervous system, can be properly designated as intraneural conditioning, as opposed to the conventional extraneural conditioning, in which the stimulus is applied outside the nervous system, usually to the distance receptor organs.

Electrical stimulation of the central nervous system of the intact, unanesthetized animal is easily accomplished by a new technic used in this laboratory (Loucks [5]). Electrodes which may be placed in contact with nerve tissue are connected to a small, collodion-coated coil, which, in turn, is buried beneath the skin. When a primary coil, which is connected to a thyratron generator, is placed over the buried coil, the tissue at the electrodes is stimulated by the current induced in the buried coil.

CEREBELLAR CONDITIONED REFLEXES

A study of intraneural conditioning may concern (1) which elements of the unconditioned reflex or (2) which elements of the conditioned reflex may be eliminated with preservation of conditioned reflex function.

A summary of the results obtained previously by the elimination of the peripheral and various central parts of the reflex arc follows (Light and Gantt [6]; Gantt [7]).

1. *Elimination of Efferent Structures.*—In 4 dogs the right hindleg was paralyzed by crushing the anterior nerve roots between the exit from the lamina interna of the dura mater and the junction with the posterior root. Before regeneration of the injured motor nerves, elaboration of a simple conditioned reflex (withdrawal of the leg to electrical shock) was attempted on the paralyzed side, although the animal was, of course, unable to make the actual movement of the paralyzed limb. When the generalized conditioned response (minus its specific component) became well established, as shown by howling and motor defense reactions, the training was discontinued—in each dog before any evidence of regeneration. After regeneration the conditioned signal was given always without shock, and was followed by withdrawal of the formerly paralyzed leg—the appropriate and specific conditioned movement, but one which was never possible during the period of training.

2. *Elimination of Afferent Structures.*—(*a*) Elimination of the Afferent Analyzer (Peripheral) of the Unconditioned Reflex: A reflex movement of the hindleg was obtained by stimulating directly the dorsal root of a lumbar nerve. The stimulus was applied directly to the dorsal nerve to furnish the unconditioned reflex (movement of the leg), instead of, as in the usual experiment, applying shock to the skin of the leg to cause withdrawal. As in the ordinary conditioned

5. Loucks, R. B.: (*a*) A Preliminary Report of a Technique for Stimulation or Destruction of Tissues Beneath the Integument and the Establishing of Conditioned Reactions with Faradization of the Cerebral Cortex, J. Comp. Psychol. **16**:439-444, 1933; (*b*) A Technique for Faradic Stimulation of Tissues Beneath the Integument in the Absence of Conductors Penetrating the Skin, ibid. **18**:305-313, 1934; (*c*) The Experimental Delimitation of Neural Structures Essential for Learning: The Attempt to Condition Striped Muscle Responses with Faradization of the Sigmoid Gyri, J. Psychol. **1**:5-44, 1936.

6. Light, J. S., and Gantt, W. H.: Essential Part of Reflex Arc for Establishment of Conditioned Reflex, J. Comp. Psychol. **21**:19-36, 1936.

7. Gantt, W. H.: Contributions to the Physiology of the Conditioned Reflex, Arch. Neurol. & Psychiat. **37**:848-858 (April) 1937; Anatomical Structures Involved in Conditioned Reflex Elaboration, Kongressber. des XVI. Internat. Physiol. Kong., Zürich **2**:116, 1938.

reflex experiment, the shock to the dorsal root was preceded by a buzzing sound. After a few combinations the signal (buzzer) evoked the same movement as the induced shock to the dorsal root; that is, a conditioned reflex could be elaborated to a central excitation as easily as to the corresponding peripheral stimulus.

Similar experiments were performed on 3 dogs using stimulation of the posterior columns of the spinal cord at about the level of the sixth lumbar nerve. The induction shock to the cord was preceded for one second by a conditioned stimulus (buzzer). The unconditioned reflex was a movement, usually flexion of the ipsilateral hindleg, to stimulation of the cord by the induction shock. In all these dogs there was a conditioned reflex to the buzzer, consisting of general tension plus movement of the hindleg, which appeared first on reenforcement 107 (sixth day), reenforcement 120 (seventh day) and reenforcement 422 (twenty-second day) in the 3 animals, respectively.

Stimulation of the sigmoid gyrus to give a leg movement was performed in this laboratory by a collaborator.[5c] In 3 dogs which received about 600 reenforcements of the conditioned stimulus with the faradic shock to the motor cortex, there was no evidence of the formation of a conditioned reflex.

(*b*) Elimination of the Afferent Member of the Conditioned Reflex: The food-conditioned reflex was formed to stimulation of the area striata.[5c] Stimulation of the motor area of the cerebral cortex was used in the preceding experiments as a successful signal for the cutaneous shock of the left foreleg.

In the present experiments part of the unconditioned reflex arc was eliminated by applying the unconditioned stimulus to the cerebellum to obtain a cerebellar reflex movement, the conditioned reflex arc being the intact conventional one.

The cerebellum was chosen in this study for two reasons. First, it is an easily accessible organ having characteristics of a suprasegmental structure, but at the same time it is on a definitely lower level than the cerebral cortex. Second, the integrative function of the cerebellum remains a puzzle, in spite of the significant recent work of Bard,[2] Clark and his associates,[8] Ranson and his associates,[9] Larsell, cited by Fulton,[10] and others. A resolution of the question whether conditioned reflexes can be elaborated on the basis of the movement initiated by stimulating the cerebellum, i. e., an intraneural cerebellar unconditioned reflex, might throw considerable light on both the integrative function of the

8. Ward, J. W., and Clark, S.: Specific Responses Elicitable from Subdivisions of the Motor Cortex of the Cerebrum of the Cat, J. Comp. Neurol. **63:** 49-64, 1935. Clark, S. L.: Responses Following Electrical Stimulation of the Cerebellar Cortex in the Normal Cat, J. Neurophysiol. **2:**19-35, 1939.

9. Magoun, H. W.; Hare, W. K., and Ranson, S. W.: Electrical Stimulation of the Interior of the Cerebellum in the Monkey, Am. J. Physiol. **112:**329-339, 1935. Hare, W. K.; Magoun, H. W., and Ranson, S. W.: Electrical Stimulation of the Interior of the Cerebellum in the Decerebrate Cat, ibid. **117:** 261-266, 1936.

10. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

cerebellum and the question concerning what parts of the reflex arc can be eliminated with preservation of conditioned reflex function. The question to be answered, then, is: Can a cerebellar movement (unconditioned) initiated by a faradic stimulus applied to the cerebellar tissues (intraneurally) be made a conditioned reflex, that is, an intraneural conditioned reflex?

EXPERIMENTAL PROCEDURE

Small dogs (weight, 6 to 8 Kg.) were used because the operative procedure was more easily carried out and because the conditioning apparatus was so con-

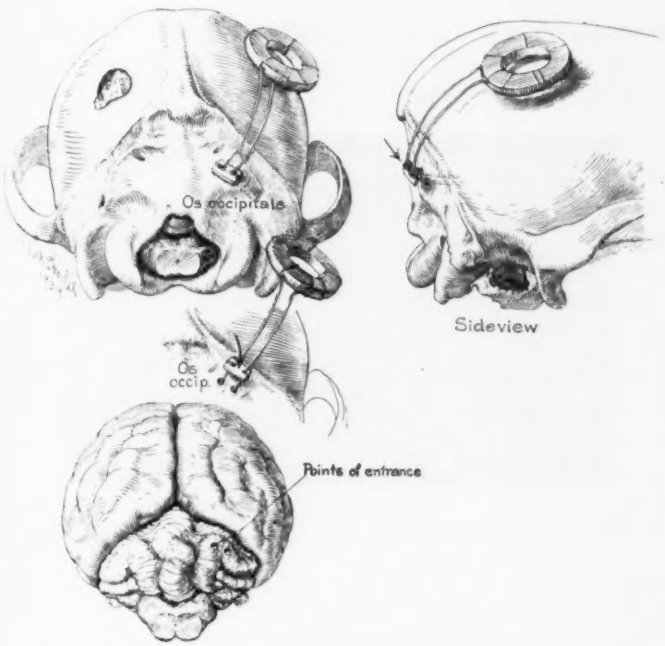


Fig. 1.—Insertion of electrodes.

structed that it could accommodate only small animals. A collodion-coated coil (figs. 1 and 2) was embedded beneath the skin over the temporal muscle; silver electrodes, insulated by several coats of collodion, ran from the coil to the point to be stimulated, e. g., the cerebellum. The bared tips of the electrodes were inserted through two holes in the bone, which had been located by the external markings of the skull. On the following day, when the animal had recovered from the effects of the ether, it was suspended in a hammock-like apparatus, which permitted rather free movement of the limbs and musculature. An external field coil was fastened on the animal's head directly over the buried secondary coil and was energized by a thyratron generator.[3] The buried coil

thus absorbed energy from the field coil, with which it had no direct connection, just as the secondary coil of a transformer is activated by its primary. The intensity of the stimulus at the electrodes in cerebellar issue was gradually increased by increasing the amplitude of the output of the thyratron generator until a noticeable muscular response was evoked. If no observable response was elicited when the stimulus was at a maximum, that particular animal was discarded. In many cases no response could be elicited after operation. There were a number of conditions which might account for the lack of response. The electrodes might be in "silent," or nonexcitable, cerebellar tissue. Breakage of the electrodes, damage to the insulation or slippage of the electrodes from their original position, accidents occurring either singly or together, resulted in lack of response to stimulation.

When stimulation of the cerebellum produced a response, at least two observers made notation of the character of the responses thus evoked. Thereon training was instituted to condition this cerebellar response to either an auditory or a

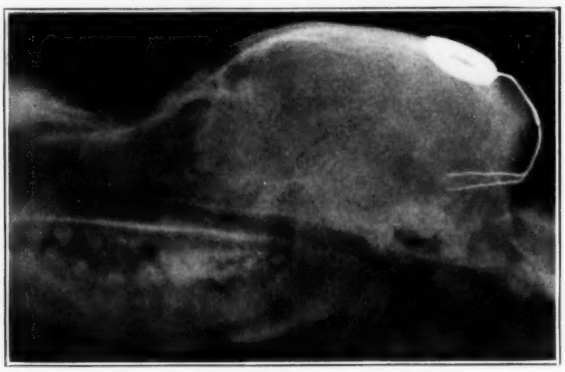


Fig. 2.—Roentgenograms, showing position of electrodes.

visual stimulus, stimuli which did not natively produce the responses evoked by stimulation of the cerebellum. The conditioned stimulus, of two seconds' duration, was presented before training was started to insure its indifference for elicitation of the cerebellar response. The output of the thyratron stimulator was adjusted to an intensity just strong enough to give a response. This minimum intensity of the unconditioned stimulus was always used in order to prevent the possible spread of the stimulating current to adjacent neural structures. Each conditioning session consisted of 20 paired stimulations of the conditioned stimulus (light or bell, two seconds' duration) and the unconditioned stimulus (faradic shock to the cerebellum, one-tenth second's duration and occurring at the end of the conditioned stimulus). Anticipatory responses, responses similar in character to the unconditioned responses which were evoked by the conditioned stimulus, were scored as conditioned responses. If no anticipatory responses appeared after several training sessions, test trials in which the unconditioned stimulus was omitted were presented in order to see whether simultaneous conditioning had

developed. If after several hundred trials there was no evidence of either anticipatory or simultaneous conditioning, training was discontinued, and the cerebellar response of that particular animal was considered not subject to modification by conditioning. On the other hand, if evidence of conditioning appeared in the early training periods, further training was given until conditioning was well established, the formal criterion being a 100 per cent conditioned response for one training period (20 conditioned responses in 20 paired stimulations). When this criterion had been attained, the experimental conditions were changed to see whether the usual phenomena of conditioning (experimental extinction; conditioned differentiation, etc.) would result.

EXPERIMENTAL RESULTS

Responses Evoked by Cerebellar Stimulation.—The responses elicited by faradic stimulation of the cerebellum may be conveniently divided into three categories: (1) movements of the ipsilateral limbs; (2) contraction of the ipsilateral neck and shoulder muscles, both deep and superficial, and (3) movements of isolated ipsilateral structures, such as the eyelid and pinna. Since the responses listed under any one of the categories were neither uniform from animal to animal nor from time to time in the same animal, it is desirable that the responses be described in some detail for each of the three classifications. In the group of 6 animals giving responses falling in the first category (dogs 173, 175, 176, 177, 183 and 184), flexion of the ipsilateral forelimb alone or flexion of both the forelimb and the hindlimb on the same side resulted from cerebellar stimulation. In most animals both types of response were evoked at one time or another. In a few cases the only response to cerebellar stimulation was flexion of the ipsilateral forelimb. Since the primary goal of these investigations was the conditioning of the cerebellar responses, not all of the animals in which responses were evoked were examined microscopically for positions of the electrodes. In general, when limb movements were evoked, the electrodes were found in the cortex or the subcortex of the medial aspect of the crus primum of the lobulus ansiformis. In some cases one electrode was in the vermis and the other in the crus primum.

The second category represented by far the largest number of animals and showed the widest variation in the character of the responses. With 5 of the 11 animals in this group (dogs 182, 190, 192, 194 and 195) activation of the buried coil resulted in the contraction of ipsilateral deep neck muscles, which caused jerking of the shoulder and swinging of the ipsilateral forelimb. With 4 animals of this group (dogs 138, 189, 191 and 197) faradic stimulation elicited contraction of an ipsilateral deep neck muscle without any concomitant response. The

remaining 2 animals must be considered separately. With 1 (dog 205) activation of the buried coil resulted in opening of the mouth and raising of the larynx. With the other (dog 200) stimulation produced rotation of the head toward the same side of the body. The general locus of the electrodes for this group of animals was in the ventral aspect of the vermis, somewhat lateral to the midline.

Only 2 animals were included under the third category. Both gave discrete, but dissimilar, responses. With 1 (dog 201) stimulation of the cerebellum produced sharp, complete closure of the ipsilateral eyelid. With the other (dog 206) activation of the cerebellar coil elicited wigwagging of the ipsilateral pinna. Macroscopic examination of the cerebellum of dog 206 showed the electrodes to be in the vermis, in the same general locus as that reported for the animals of the second group. The locus of the electrodes of dog 201 could not be determined.

Conditioning of Responses Evoked by Cerebellar Stimulation.—Not all responses elicited by electrical stimulation of the cerebellum could be conditioned. Those responses which in the preceding section were listed under the first and third categories were much more susceptible to modification by the conditioning procedure than were those listed under the second category. Since the results obtained by conditioning were so variable, they can best be presented by giving the abbreviated protocols of the experiments with those animals in which conditioned responses were elaborated.

Dog 173.—The unconditioned response was variable; most of the time it consisted of flexion of the ipsilateral forelimb, but sometimes flexion of both the ipsilateral hindlimbs occurred. The sound of an electric doorbell was used as the conditioned stimulus. The first conditioned response appeared on the third trial. Conditioning reached 100 per cent in the second training session. Continuation of training maintained a high level of conditioning for an additional 5 test periods, whereon the frequency of conditioned responses began to decrease. By the thirteenth test period the conditioned response had disappeared completely, in spite of the fact that the unconditioned stimulus on each trial evoked a clearcut flexion of the ipsilateral forelimb. Four more training sessions failed to reestablish conditioning. No further experiments were performed with this animal. The conditioned response was more variable than the unconditioned response. Flexion of the ipsilateral forelimb was the prominent characteristic of the conditioned response, although at times it might be accompanied by flexion of the ipsilateral hindlimb or by flexion of the ipsilateral hindlimb and the contralateral forelimb and hindlimb (figs. 3 and 4).

Cerebellar Lesions: Two small spherical cavities caused by the stimulating electrodes were surrounded by a zone in which there was pronounced mobilization of the microglia and macroglia. The cerebellar cortex overlying these lesions showed degeneration of ganglion cells and proliferation of the microglia in the

white matter of the cortical folia. Both lesions were located well within the subcortical white matter. The surrounding subcortical area peripheral to these lesions and the adjacent cerebellar cortex were normal in appearance.

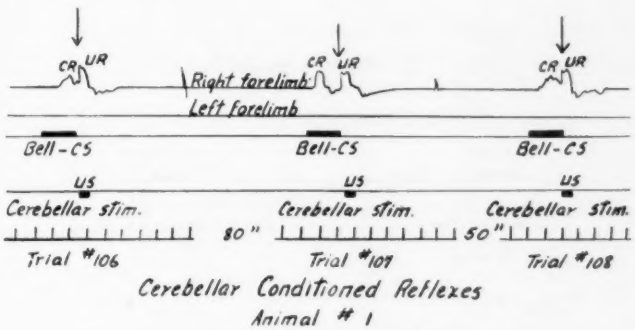


Fig. 3.—Cerebellar conditioned reflexes, dog 173.

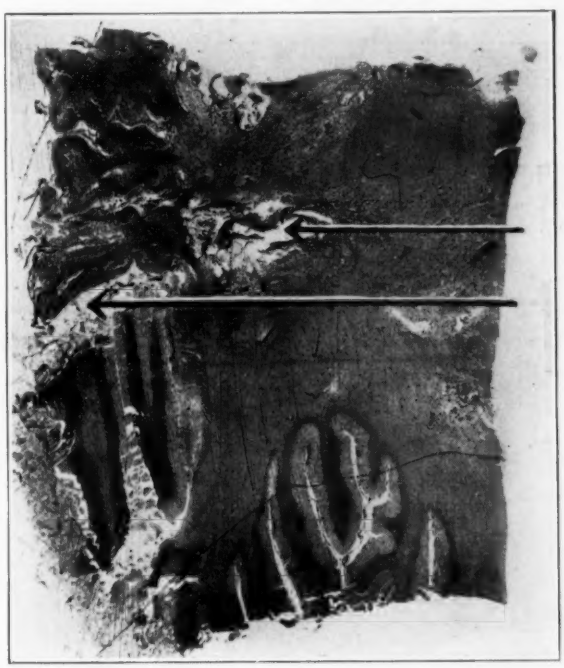


Fig. 4.—Section of cerebellum, dog 173.

Dog 177.—The unconditioned response evoked by cerebellar stimulation of this animal was a discrete flexion of the ipsilateral forelimb. Training was begun with the sound of a bell as the conditioned stimulus. The first conditioned response was observed on the thirteenth trial. A conditioned response score of 20 per cent was obtained for the first test period, 75 per cent for the second and 100 per cent

for the third. With conditioned flexion of the forelimb to the bell elaborated, training was instituted to set up a conditioned differentiation. Ten trials of the bell alone (no reenforcement with the unconditioned stimulus) and 10 trials

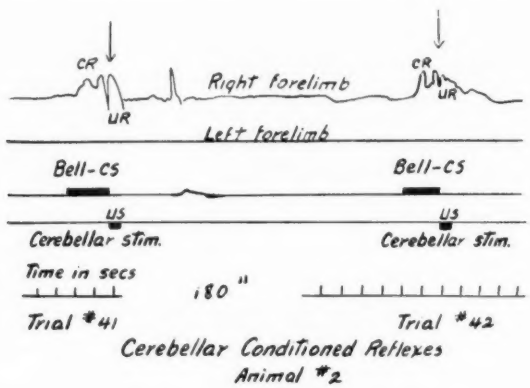


Fig. 5.—Cerebellar conditioned reflexes, dog 177.

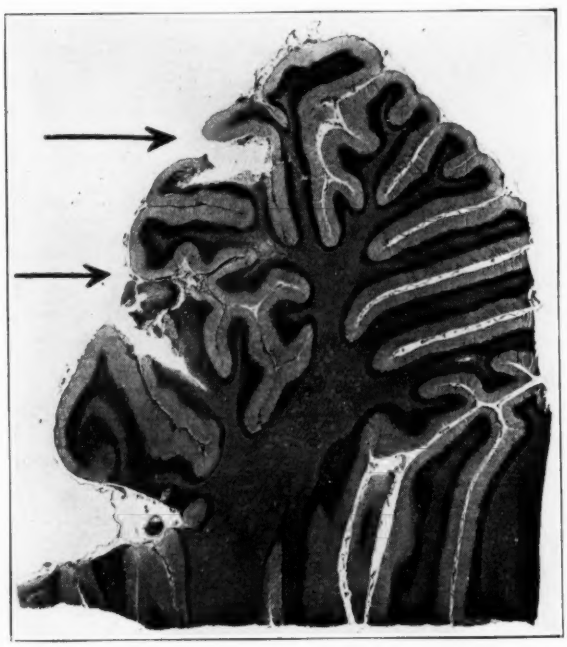
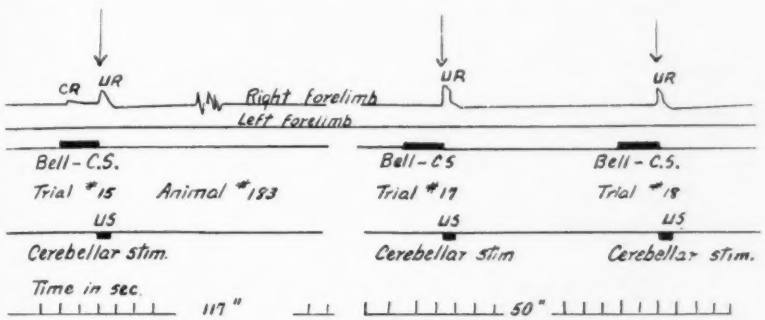


Fig 6.—Section of cerebellum, dog 177.

of a 1000 cycle tone paired with faradic shock to the cerebellum were presented in random order during each test period. Conditioned flexion to the tone was established rapidly, being 100 per cent on the fourth test period devoted to discrimination. This animal died before conditioned discrimination had been established. On the eleventh test period, which was the last before its death, the conditioning

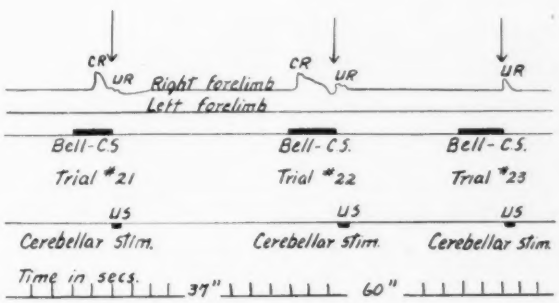
score to the bell was 70 per cent and that to the tone 90 per cent. The conditioned response was more variable than the unconditioned reflex. Whereas the latter was a discrete flexion of the ipsilateral forelimb, the conditioned response was sometimes flexion of the ipsilateral forelimb and sometimes flexion of both ipsilateral limbs (figs. 5 and 6).

Cerebellar Lesions (dog 177): A small lesion involved one of the folia of the cerebellar cortex. The ganglion cells of the molecular and granular layers



Cerebellar Conditioned Reflexes
Early Stage

Fig. 7.—Cerebellar conditioned reflexes, early stage, dog 183.



Cerebellar Conditioned Reflexes
Late Stage
Animal #183

Fig. 8.—Cerebellar conditioned reflexes, late stage, dog 183.

of the cortex showed degeneration, with some mobilization of the microglia and the macroglia in this circumscribed cortical zone. More caudally in this series of slides there was a large subcortical lesion, which involved the subcortical white matter and the peripheral part of the dentate nucleus. The large multipolar ganglion cells of the dentate nucleus over this lesion showed pyknotic changes and were shrunken. The neuroglia in this lesion and its vicinity showed little inflammatory reaction. The cerebellar cortex adjacent to the cortical lesion, the tissue in the vicinity of the subcortical lesion and the dentate nucleus adjacent to the subcortical lesion were normal in cellular topography.

Dog 183.—The unconditioned stimulus evoked a clearcut, discrete flexion of the ipsilateral forelimb in this animal. Conditioning of this response to the sound of a bell proceeded rapidly, with the first conditioned response occurring on the fourth trial. The conditioned response score for the first test period was 40 per cent, for the second 50 per cent and for the third 100 per cent. The conditioned response was almost an exact duplicate of the unconditioned reflex; flexion of the ipsilateral forelimb was never accompanied by flexion of any of the other limbs. The conditioned response was next extinguished by presenting the bell alone, without the faradic shock to the cerebellum. For successive test periods the conditioned response scores were 50, 5, 5 and 0 per cent. At some time during the extinction series one of the electrodes was broken, for after the extinction of the conditioned

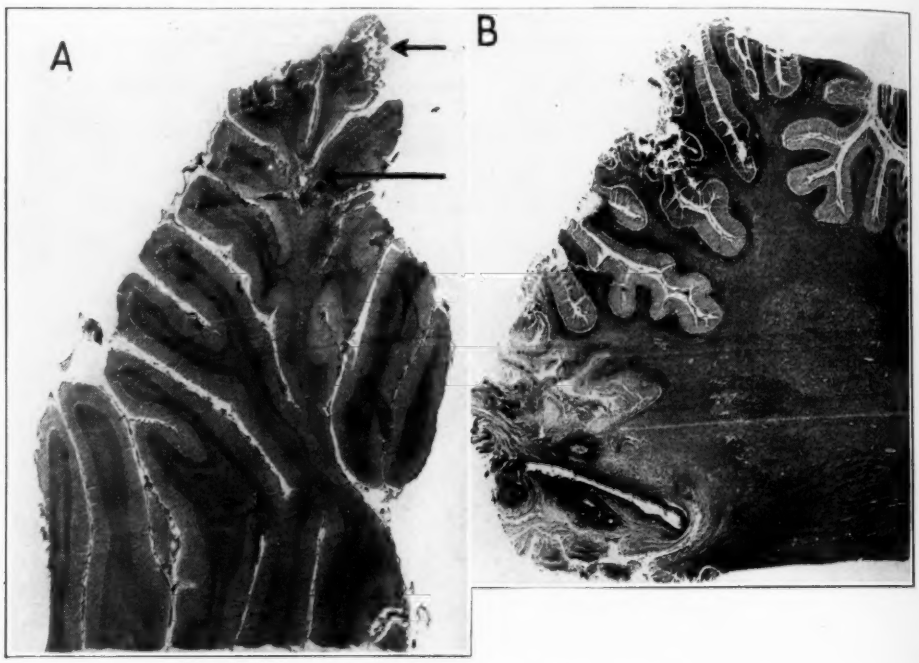


Fig. 9.—Sections of the cerebellum, dog 183.

response the unconditioned reflex could not be elicited by shock to the cerebellum. No further work could be done with this animal (figs. 7, 8 and 9 *A* and *B*).

Cerebellar Lesions (fig. 9): There was one small spherical lesion in the subcortical white matter, surrounded by a narrow zone of microglial infiltration, with some new vessel proliferation. Peripheral to this zone the cerebellar tissue was normal. The cerebellar tissue showed degeneration. Lying deep to this area were a small area of subcortical degeneration in the white matter and a circumscribed zone of microglial and macroglial proliferation. The adjacent cortex and the subcortical white matter were normal in appearance.[11]

11. Dr. F. J. Warner helped in these histologic studies.

Dog 195.—Activation of the buried coil in this animal provoked a contraction of the ipsilateral deep neck musculature, which in turn produced swinging of the ipsilateral forelimb. Conditioning was started by pairing the sound of a bell with a shock stimulus to the cerebellum. The first conditioned response occurred on the fourth trial. The score for the first period was 45 per cent, for the second 85 per cent and for the third 100 per cent. The conditioned response differed considerably from the unconditioned response. Its most prominent feature was flexion of the ipsilateral forelimb. Flexion of any of the other limbs might accompany flexion of this limb. At no time did the conditioned response include contraction of any of the neck musculature involved in the unconditioned reflex. With conditioning to the bell established, training was started to condition the response to the flash of an electric light. The conditioned response score for the first test period was 10 per cent, for the second 60 per cent and for the third 100 per cent. The light and the bell stimuli were now presented in random order, ten times in each test period, the light being reenforced and the bell unreenforced by the unconditioned stimulus in order to establish a conditioned differentiation. The conditioned response was 100 per cent to both the bell and the light for the first 2 training sessions. Thereafter the conditioned response to the bell was extinguished; on the fifth test period a response score of 0 was made to the bell and of 90 per cent to the light. No further work could be done with this animal, since the medial electrode had slipped from its insertion and was no longer in contact with the cerebellar tissues.

Dog 200.—Stimulation of the cerebellum evoked an unconditioned reflex, which consisted of a contracture of the ipsilateral deep neck musculature in such a manner that the head was rotated toward the ipsilateral side of the body. Conditioning to the bell was 20 per cent for the first test period, 80 per cent for the second, 70 per cent for the third and 90 per cent for the fourth. The conditioned response was a rotation or lifting of the head toward the contralateral side of the body, just opposite in direction to the unconditioned response. Differentiation was established, the bell being the negative conditioned stimulus and a 1000 cycle tone the positive conditioned stimulus. The conditioned response score on the fourth, and final, test period for differentiation was 0 to the bell and 90 per cent to the tone.

Dog 205.—Activation of the buried coil in the cerebellum of this animal produced a contraction of the ipsilateral deep neck musculature, which in turn resulted in opening of the mouth and raising of the larynx. The first conditioned response to the sound of the bell occurred in the fifth trial of the second test period. Conditioning proceeded by test periods as follows: first test period, 0; second test period, 55 per cent, and third test period, 100 per cent. The conditioned response was similar to the unconditioned response. Opening of the mouth was always observed; raising of the larynx was not observed so frequently, probably owing to difficulty in making the observations.

This animal was killed in a fight with its cage mates. Owing to bites around the head, the buried coil was torn from its moorings and broken. It was impossible to determine the location of the electrodes in the cerebellar tissue.

Dog 201.—The unconditioned response of this animal was closure of the ipsilateral eyelid. Sometimes the contralateral eyelid also closed in conjunction with the ipsilateral one. The first conditioned response to the bell was observed on the twelfth trial. A score of 15 per cent was made in the first test period, 60 per cent in the second, 35 per cent in the third, 60 per cent in the fourth, 85 per cent in the fifth and the sixth and 100 per cent in the seventh. The conditioned

response was almost an exact duplicate of the unconditioned response. It consisted of closure of the ipsilateral eyelid, sometimes accompanied by the contralateral eyelid. Conditioned differentiation was tried, with only slight success. The bell was made the negative conditioned stimulus and a 1000 cycle tone the positive conditioned stimulus. On the eighteenth test period the conditioned response scores were 30 per cent for the bell and 100 per cent for the tone. No further tests could be made owing to breakage of one of the electrodes.

The locus of the electrodes could not be determined, as no postmortem study was made on this animal.

Dog 206.—Activation of the buried coil in the cerebellum of this animal elicited a twitch of the ipsilateral pinna backward, toward the midline. The conditioning of this response proceeded rapidly. The first conditioned response to the bell was observed on the sixth trial. The conditioned response score for the first test period was 70 per cent, for the second 85 per cent and for the third 100 per cent.

Macroscopic examination showed the electrodes to be in the ventral aspect of the vermis, several millimeters from the midline. Exact location was impossible, owing to the growth of scar tissue around the electrodes.

The outstanding feature of the performances of these animals was the rapidity with which the cerebellar responses became conditioned. In 5 of the 7 animals the frequency of conditioned responses reached the criterion of 100 per cent in 40 to 60 trials (2 to 3 test periods). Flexion of the forelimb in the dog, evoked by shock stimulus to the forepaw, was ordinarily conditioned to the sound of a bell in from 240 to 260 trials.[12] Experimental extinction and the conditioning of the response to a second conditioned stimulus occurred with the proper experimental conditions. Conditioned differentiation could be established with approximately the same ease as with other conditioned responses.

COMMENT

The importance of the cerebellum as a suprasegmental structure was emphasized by Cobb.[13]

> Its greatest development, however, is only found in those mammals that have unilateral, skilled movements of the hands (apes and man). It is noteworthy that the increase in size of the cerebellar hemispheres runs parallel phylogenetically with the increase in size of the cerebral hemispheres and have intimate fiber connections with the fore-brain, via the superior peduncles and pons. So in man the greater part of the cerebellum can be considered as related to the "new motor system."

While the results obtained in this investigation demonstrate that responses elicited by faradic stimulation of the cerebellum can be condi-

12. Brogden, W. J., and Gantt, W. H.: Cerebellar Conditioned Reflexes, Am. J. Physiol. **119**:277-278, 1937.

13. Cobb, S.: Foundations of Neuropsychiatry, Baltimore, William Wood & Company, 1941, p. 60.

tioned, they shed little light on the factors responsible for the conditioning. Why are some cerebellar movements susceptible to conditioning, while others from the cerebellum, as well as movements evoked by faradic stimulation of the cerebral cortex, cannot be conditioned? Satisfactory answers to these questions can be obtained only by further experimentation, but a discussion of the possible factors involved should serve a useful purpose in the interpretation of the results already obtained.

Loucks [5e] attributed failure of animals to show conditioning of flexion of the hindlimb evoked by faradic stimulation of the sigmoid gyrus to the lack of an emotional component in the response evoked by the unconditioned stimulus. He showed that lifting of the hindlimb to cortical shock was an adequate basis for conditioning if each movement was rewarded with food. Such conditioning was attributed to the mechanism of backward association,[14] for once the response to the buzzer was experimentally extinguished, the animals failed to be reconditioned if the food was omitted. Masserman [15] used the same argument in explaining the failure to obtain conditioned emotions from stimulation of the hypothalamus. While much experimentation supports the "law of effect" as the principle of conditioning, no single principle, such as that of effect, substitution or expectancy,[16] can account for all the phenomena of learning. (For an excellent discussion of this problem see Hilgard and Marquis.[17])

If the law of effect (the stamping in of movements under the influence of pain or pleasure) were basic to all learning, then none of our cerebellar animals should have become conditioned. Pain was no more a factor in the responses produced by cerebellar stimulation than in those produced by stimulation of the cerebral cortex. Proprioceptive sensory experience was also of the same order in both instances. Since there was no more of an emotional component in the cerebellar reflexes than in the reflexes produced by shock to the cortex, the law of effect cannot be a factor in the conditioning of the cerebellar responses.

The obvious difference between Loucks's and Masserman's experiments and our own is in the locus of the electrodes The difference in

14. "Backward conditioning" is the process of forming a conditioned response by having the conditioned stimulus follow, rather than precede, the unconditioned reflex to which it is related.

15. Masserman, J. H.: Is the Hypothalamus a Center of Emotion? Psychosom. Med. **3**:3-25, 1941.

16. Stephens, J. M.: Expectancy vs. Effect—Substitution as a General Principle of Reinforcement, Psychol. Rev. **49**:102-116, 1942.

17. Hilgard, E. R., and Marquis, D. G.: Conditioning and Learning, New York, D. Appleton-Century Company, Inc., 1940.

the results is, then, reduced to a difference in the functions of the motor cortex (or hypothalmus) and those of the cerebellar loci which were stimulated in our animals that became conditioned. From what is known at present of the function of the cerebellum, it is impossible to determine what are the factor or factors which are essential for the conditioning of cerebellar movements.

Luciani's and Sherrington's statement that the cerebellum functions as an undifferentiated whole has been laid open to question by the recent work on localization, as well as by the fact that in our experiments on stimulation of the cerebellum only from certain areas could movements be elicited; furthermore, that not all of the cerebellar movements in our animals could be conditioned is added evidence for sharp localization. That it was not a question of intensity of stimulation was ruled out in our experiments, for whenever the movements could be conditioned, the conditioning occurred with almost equal speed regardless of intensity of shock, allowance being made for differences between individual animals.

It seems likely that whether or not conditioning of the cerebellar responses is to occur depends on the differential functioning of various parts of the cerebellum.

It is not surprising that functions arising from the neocerebellum can be conditioned. Owing to the limited area which we stimulated, the experiments here afford no comparison between the neocerebellum and the paleocerebellum. However, another function closely related to cerebellar movements, and probably connected with the paleocerebellum, has been conditioned in this laboratory, viz., the loss of balance by galvanic stimulation of the vestibular apparatus (Löwenbach and Gantt [18]).

In these experiments, as well as in those reported in the present paper, a conditioned response was formed on the basis of a certain inborn reflex in a nervous structure generally considered as controlling automatic movements. On the other hand, conditioned *stimuli* have been formed from electrical or other excitations in both the cerebral and the subcortical systems—excitations which are ordinarily considered as "subconscious." Thus stimulations of the cerebral cortex (Loucks [5c]; Gantt [7]) and of the vestibular apparatus (Spiegel and Oppenheimer [19]) have been used as conditioned stimuli. Whether the cerebellum has

18. Löwenbach, H., and Gantt, W. H.: Conditioned Vestibular Reactions, J. Neurophysiol. **3**:43-48, 1940.

19. Spiegel, E. A., and Oppenheimer, M. J.: Conditioned Reactions to Position and Angular Acceleration, Am. J. Physiol. **125**:265-275, 1939.

this kind of integrative function, in addition to the type under discussion in this article, has not yet been determined.

Whether movements elicited in the present experiments are independent cerebellar functions or, like the conditioned responses obtained on the basis of intraneural stimulation of the spinal cord, are mediated through the cortex, is a problem for future investigation.

Our experiments neither eliminate nor prove the participation of the cerebral cortex in the formation of the conditioned reflexes. It is possible that the movement initiated by stimulating the cerebellum has a definite representation in the cerebral cortex through the brachium conjunctivum, the thalamus and the cerebral cortex and that the functional connection between the afferent limb of the conditioned stimulus and the efferent limb of the unconditioned reflex is made either in the thalamus or somewhere in the cerebral cortex. To resolve this question recourse must be had to the method of extirpation. But the work of former investigators lends some support to such a view, as is seen from the following considerations.

The part of the cerebellum stimulated in these experiments was usually the lobulus ansiformis, with its fibers converging on the nucleus dentatus, i. e., the neocerebellum. From here there are pathways connecting with the nucleus ruber and the thalamus; according to Dow [20] and Curtis,[21] the cerebral cortex, areas 4 and 6, is connected with the cerebellum. Curtis, on electrical stimulation of the motor area of the cerebral cortex, and Dow, on stimulation of the pons, traced pathways chiefly to the lobulus ansiformis. Moreover, Rossi [2] showed that stimulation of the lobulus ansiformis results in exaggerated excitability of the opposite cerebral motor cortex. Walker "demonstrated that the spontaneous electrical activity of this part of the cortex is markedly increased by a contralateral cerebellar stimulation." Bard [2] expressed the belief that the cerebellum is intimately connected phylogenetically with the cerebral cortex, representing, with the pons and the thalamus, "a huge chain of internuncial neurons." Clinical correlations indicate an intimate connection between the cerebellum and the cerebral cortex. Walshe [22] pointed out that cerebellar lesions give rise to disorders of voluntary movement only and that there is no cerebellar ataxia in a reflex preparation. He suggested that the cerebellum acts in some

20. Dow, R. S.: Efferent Connections of the Flocculonodular Lobe in Macaca Mulatta, J. Comp. Neurol. **68**:297-305, 1938.

21. Curtis, H. J.: Cerebellar Action Potentials in Response to Stimulation of Cerebral Cortex, Proc. Soc. Exper. Biol. & Med. **44**:664-668, 1940

22. Walshe, F. M. R.: The Significance of the Voluntary Element in the Genesis of Cerebellar Ataxia, in discussion on Symposium on the Cerebellum, Brain **50**:377-385, 1927.

relation to the synthesizing function of the cerebral cortex. Smyth [23] observed that in a case of disease of one frontal lobe the contralateral nucleus dentatus showed pathologic cell changes. All these results, as well as previous work in this laboratory on intraneural conditioning, makes not improbable the elaboration of conditioned reflexes from cerebellar stimulation.

There is thus another piece of evidence that many subconscious, or even supposedly subcortical, functions are capable of being conditioned, while other subcortical, or even cortical, functions (e. g., movement of the leg through stimulation of the motor cortex) have not been conditioned. The results are at present seemingly paradoxic from the point of view both of the nature of the function ("voluntary," automatic, etc.) and of its anatomic locus. Psychologic explanations, such as the "law of effect," pain-pleasure and teleologic principles, are not applicable; the principle stated by Gantt and associates [24] of the necessity for a central excitation in the higher nervous centers, while explaining why some reactions can be conditioned, does not explain why certain movements are more readily conditioned than similar and closely related ones.

While conditioning of the cerebellar reflexes points to an integrative action on the part of the cerebellum, we have yet insufficient knowledge of the cerebellum and its pathways to account wholly for this behavior in terms of neuroanatomy and neurophysiology.

SUMMARY

These experiments represent a study of intraneural conditioned responses established from movements initiated in the cerebellum. The cerebellar movements were produced by stimulation of the neocerebellum in chronic preparations (dogs), with induced electrical currents. The movements elicited were contractions of the ipsilateral ear, neck or shoulder muscles; with moderate electric shock they occurred without evidence of pain or disturbance to the animal.

Such movements were made the basis for conditioned responses by preceding the electric shock with a bell or light. Both excitatory and

23. Smyth, G. E.: The Significance of Lesions in the Dentate Nuclei Apparently Consecutive to Disease of the Frontal Lobes, Brain **64**:63-72, 1941.

24. Gantt, W. H.: Contributions to the Physiology of the Conditioned Reflex, Arch. Neurol. & Psychiat. **37**:848-858 (April) 1937. Gantt, W. H.; Katzenelbogen, S., and Loucks, R. B.: An Attempt to Condition Adrenalin Hyperglycemia, Bull. Johns Hopkins Hosp. **60**:400-411, 1937. Katzenelbogen, S.; Loucks, R. B., and Gantt, W. H.: An Attempt to Condition Gastric Secretion to Histamin, Am. J. Physiol. **128**:10-12, 1939. Löwenbach, H., and Gantt, W. H.: Conditioned Vestibular Reactions, J. Neurophysiol. **3**:43-48, 1940.

inhibitory conditioned responses could be formed from the cerebellum with the same ease that they can be formed by using a painful shock applied to the skin of the leg.

Thus intraneural conditioned responses can be established on the basis of cerebellar movements. The cerebellum may have an independent higher integrative function, or this apparent integration may be brought about through the thalamus and the cerebral cortex.

Department of Psychology, University of Wisconsin.

Johns Hopkins Hospital.

MORQUIO'S DISEASE ASSOCIATED WITH MENTAL DEFECT

MALCOLM J. FARRELL, M.D.*

JOHN D. MALONEY, M.D.*

AND

PAUL I. YAKOVLEV, M.D.

WAVERLEY, MASS.

A search of the literature has revealed that since Morquio's original description of a type of familial osseous dystrophy 43 cases of the condition have been reported in this country and abroad. Morquio[1] described 4 cases in a family of 5 children. The fifth child of this family was free of osseous dystrophy, but he was mentally defective. The father and mother were first cousins. Morquio pointed out that the bony alterations do not appear until after the first year, when the child begins to walk. The changes are painless and progressive for several months, eventually becoming stationary and permanent. The thorax, the vertebral column and the limbs become deformed, the head remaining normal. These skeletal deformities are symmetric and cause difficulty in locomotion. The patient on first sight appears as if he suffered from Pott's disease. The genu valgum, flat feet, deformity of the vertebral column and weakness of the muscles and tendons cause a peculiar, ducklike, waddling gait. There are no visceral lesions. The intelligence remains normal. The last-mentioned feature was pointed out by Morquio and subsequent authors with some emphasis.

In the detailed description of his cases Morquio laid particular stress on the following features of the disease: the dwarfism; the short neck, causing the head to appear sunken into the chest; the kyphosis; the flat feet, held wide apart when the patient stands or walks; the limitation of movement at some of the joints, as a result of bony deformities, and the excess of mobility at others. The thorax was described as short, with increased anteroposterior diameter and broad base. Roentgenograms, according to Morquio, show a profound disturbance of osteogenesis, associated with considerable diminution of the blood cal-

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From the Research Unit, the Walter E. Fernald State School.

* Dr. Farrell is now serving as Major and Dr. Maloney as Captain in the United States Army Medical Corps.

1. Morquio, L.: Sur une forme de dystrophie osseuse familiale, Arch. de méd. d. enf. **32**:129-140 (March) 1929; Sur une forme de dystrophie osseuse familiale, ibid. **38**:5-24 (Jan.) 1935.

cium. These changes in the bone include rarefaction, malformation, destruction, retardation and more or less complete absence of ossification, affecting particularly the epiphyses of all long bones.

Valentin [2] reported 2 cases of familial multiple osteochondropathy. Ruggles [3] described 8 cases, 5 of them being in one family. Additional instances were reported by Meyer and Brennemann [4] (1 case), Coward and Nemir [5] (2 brothers), Barnett [6] (2 brothers), Brown [7] (a mother and 2 brothers), Davis and Currier [8] (2 brothers), Sainz de los Terreros and Lacalle [9] (2 cases), Giraud and Bert [10] (2 brothers), Summerfeldt and Brown [11] (2 cases), Freeman [12] (1 case), Maróttoli and de Azcuenaga [13] (1 case), Pohl [14] (1 case), Crawford [15] (1 case), Jacobsen [16] (20 cases in one family, in 4 of which the author made examination), Brockema [17] (1 case), Depetris [18] (1 case), Einhorn and associates [19] (3 cases) and, most recently, Hubeny and Delano [20] (1 case).

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2. Valentin, B.: Knochensystemerkrankung (atypische Chrondrodystrophie, Ostrochondropathia multiplex) und sogenannte Platyspondylia generalisata, Zentralbl. f. Chir. **57**:2038-2050 (Aug. 16) 1930.

3. Ruggles, H. E.: Dwarfism Due to Disordered Epiphysial Development, Am. J. Roentgenol. **25**:91-94 (Jan.) 1931.

4. Meyer, F., and Brennemann, J.: A Rare Osseous Dystrophy (Morquio), Am. J. Dis. Child. **43**:123-135 (Jan.) 1932.

5. Coward, N. R., and Nemir, R. L.: Familial Osseous Dystrophy (Morquio's Disease), Am. J. Dis. Child. **46**:213-214 (July) 1933.

6. Barnett, E. G.: Morquio's Disease: Presentation of Two Cases, J. Pediat. **2**:651-656 (June) 1933.

7. Brown, D. O.: Morquio's Disease, M. J. Australia **1**:598-599 (May 15) 1933.

8. Davis, D. B., and Currier, F. P.: Morquio's Disease: Report of Two Cases, J. A. M. A. **102**:2173-2176 (June 30) 1934.

9. Sainz de los Terreros, C., and Lacalle, E.: Enfermedad de Perthes o de Morquio? Heredo-distrofia osteo-articular coxo-femoral, Arch. españ. de pediat. **18**:412-423 (July 1934.

10. Giraud, G., and Bert, J. M.: La dystrophie osseuse de Morquio dans le cadre des hyperlaxités familiales, Rev. neurol. **63**:845-856 (June) 1935.

11. Summerfeldt, P., and Brown, A.: Morquio's Disease, Arch. Dis. Childhood **11**:221-229 (Aug.) 1936.

12. Freeman, J.: Morquio's Disease, Am. J. Dis. Child. **55**:343-355 (Feb.) 1938.

13. Maróttoli, O. R., and de Azcuenaga, S.: Osteocondrodistrofia generalizata (enfermedad de Morquio), Rev. méd. de Rosario **28**:1265-1274 (Dec.) 1938.

14. Pohl, J. F.: Chondro-Osteodystrophy (Morquio's Disease), J. Bone & Joint Surg. **21**:187-192 (Jan.) 1939.

15. Crawford, T.: Morquio's Disease, Arch. Dis. Childhood **14**:70-77 (March) 1939.

16. Jacobsen, A. W.: Hereditary Osteochondrodystrophia Deformans, J. A. M. A. **113**:121-124 (July 5) 1939.

17. Brockema, H.: Rare Bone Diseases (Morquio's Disease), Maandschr. v. kindergeneesk. **9**:240-251 (March) 1940.

(Footnotes continued on next page)

REPORT OF TWO CASES

The father, a healthy, intelligent Syrian, was born in 1882. The mother, also Syrian, was born in 1889 and died of a "stomach tumor" at the age of 46. The father and mother were first cousins. Detailed inquiry revealed no deformities on either side of the family. The mother had six pregnancies. The oldest child was a male, who was well and a college graduate. The next 2 children were normal girls; the fourth pregnancy ended in a miscarriage. Next our female patient (J. H.) was born, followed by a normal girl and finally, by our male patient (E. H.).

CASE 1.—J. H. (fig. 1), a 19 year old imbecile girl, had a mental age of 3 years 6 months and an intelligence quotient of 22.

Birth was normal and development was uneventful until the age of 18 months, when she began to walk. The parents then noticed that she was deformed, and it was thought that she had "rickets." As she grew older these deformities became more pronounced; they were always painless. At the age of 13½ she was admitted to the Fernald State School because of mental deficiency.

Mental Status.—The mental status was characteristic of an adult imbecile. Her vocabulary did not exceed that of a child of 3½ years and was limited to household words and babbling sentences. She was able to dress herself and to take care of her toilet needs. She was vaguely conscious of the abnormality of her physique and on this account was ill at ease when abroad. She tended to be rather seclusive and was reticent with persons who were not a part of her everyday entourage. She readily associated with children of her mental age and stature. In spite of attempts at instruction, she never learned to read or write. However, she showed enough intellectual curiosity to browse on her own initiative over picture books for children. Her interest in and her play with the assortment of toys was at the level of her mental age, i. e., that of a child of about 3½ to 4 years. She was rather passive, complacently obedient and showed little initiative in her play with other children. Although she was physically mature, she showed only rudimentary consciousness of her sex. The span of her attention was short, and she was exceedingly distractible. When requested to keep still and to maintain a posture or to perform a series of test movements, she was restless, constantly shifted her posture and was unable to carry out a series of movements as instructed.

Physical Status.—Physically, she was a typical dwarf. Her weight was 54 pounds (24.5 Kg.), the average normal weight for her age being 117 pounds (53.1 Kg.), and her height 38½ inches (97.8 cm.), the average normal height for her age being 62 inches (157.5 cm.). The circumference of her head was 19¾ inches (50 cm.), which was 2 inches (5 cm.) less than normal. She had abundant black hair and heavy eyebrows and eyelashes. Her nose was the large aquiline nose of her race. There was marked prognathism. The lower teeth, which were widely spaced, protruded well beyond the upper teeth, so that her face resembled somewhat that of acromegaly. There was a fine, dark hirsuties over the upper lip. The neck was short, the chin almost resting on the sternum. The thyroid was not

18. Depetris, P.: Enfermedad de Morquio, Arch. argent. de pediat. **11**:369-376 (April) 1940.

19. Einhorn, N. H.; Moore, J. R.; Ostrum, H. W., and Rowntree, L. G.: Osteochondrodystrophia Deformans (Morquio's Disease), Am. J. Dis. Child. **61**: 776-794 (April) 1941.

20. Hubeny, N. J., and Delano, P. J.: Dyostosis Multiplex, Am. J. Roentgenol. **46**:336-342 (Sept.) 1941.

palpable. The thoracic cage was enlarged anteroposteriorly. The huge, pendulous breasts contrasted with her short, stunted stature. The heart and lungs were normal. The blood pressure was low, the systolic pressure being 88 and the diastolic 70. The abdomen was large, without being obese. The liver and spleen were not enlarged. Because of the shortening of the trunk, the epigastric region was protruded. The skin and subcutaneous tissues over the thoracolumbar region

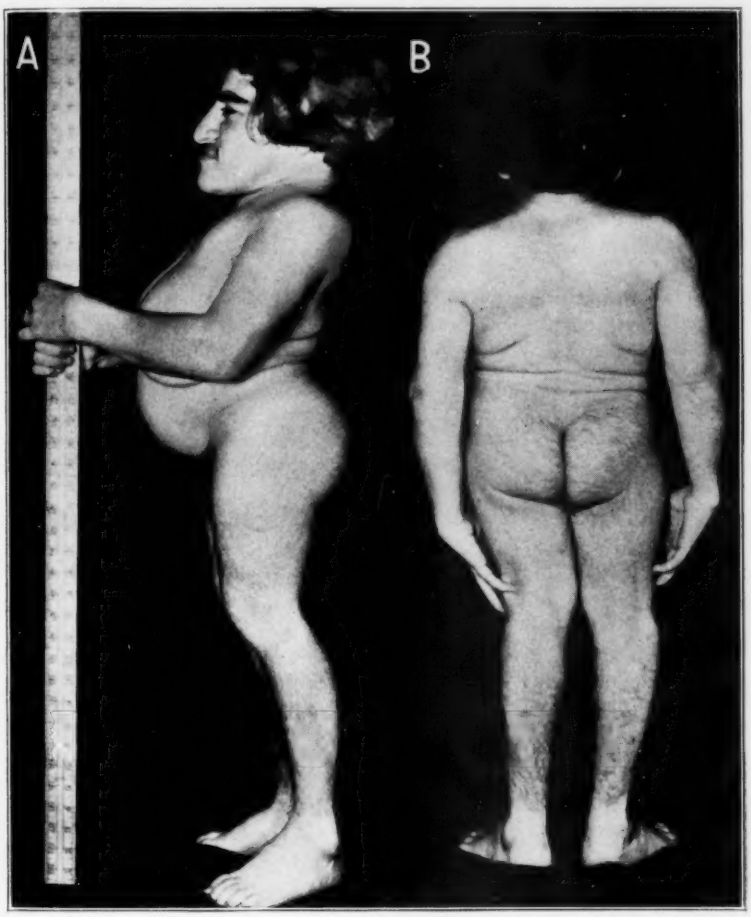

Fig. 1.—F. H. (case 1).

of the back were rolled into thick transverse folds. There were an excessive growth of hair on the arms and the lower part of the back, pronounced dorsal scoliosis, with the convexity to the right, and extreme lumbar lordosis, but no kyphosis. The extremities revealed disproportions not unlike those seen in cases of achondroplasia. The upper portions of the arms and the thighs were abnormally short, whereas the forearms, the lower portions of the legs and the hands and feet were developed as in a person of normal stature. Because of severe foreshortening of

the trunk and thighs, the finger tips reached to the knees when she was standing erect. The stunted development of the trunk and proximal segments of the extremities contrasted with the relatively normal proportions of the head and of the distal segments of the extremities and gave to the patient the grotesque appearance of a child with the head and limbs of an adult. The mobility of the shoulder joints was limited. She was unable to raise her arms above her head. The elbow joints were large and could not be completely extended. On the contrary, mobility of the hip joints was increased, particularly on the right. There were coxa vara and pes planum bilaterally. Her gait was typically waddling. While walking she held her arms in abduction backward, thrust her abdomen and pelvis forward (lordosis) and swung her body from side to side. The skeletal musculature was poorly developed, weak and lax. There were no fibrillation and no muscular atrophies but, rather, a simple hypoplasia. The cranial nerves were intact. The eye movements were free. The corneas were clear and the pupils normal. The fundi were rather pale and the retinas less pigmented than one would expect in a person of her race and complexion. The tests for visual acuity could not be carried out with any degree of accuracy, but no gross visual defect was in evidence. The tendon reflexes were all present and equal on the two sides. The plantar reflex was of flexor type bilaterally. There was no asynergia or other signs of the cerebellar series. Sensory disturbances were absent. The abnormalities of the gait and posture were readily attributable to the skeletal deformities. Her menses were not established until the age of 16½ years. They were scant but fairly regular.

Laboratory Studies.—Urine: Urinalysis revealed a trace of albumin, numerous hyaline casts, 149 international units of androgen and 4,280 international units of estrogen per day.[21]

Blood: The erythrocytes numbered 4,200,000 and the leukocytes 9,700 per cubic millimeter, with a hemoglobin content of 82 per cent. Calcium measured 8 mg., phosphorus 4.6 mg. and cholesterol 187 mg. per hundred cubic centimeters. The Hinton test of the blood for syphilis gave negative results. It was impossible to obtain an accurate measurement of the basal metabolic rate.

The results of the roentgenologic examination of this patient are reported together with those of her brother.

Case 2.—E. H. (fig. 2), a 14 year old imbecile boy, had a mental age of 2 years 2 months and an intelligence quotient of 17. Birth was normal. The history of early development was uneventful until the age of 9 months, when he had pneumonia. He was said to be in poor health for eight months following this illness, and his physical development became retarded. He began to walk about this time, and the parents then became aware that his condition was similar to that of his sister. At the age of 2 years he was examined in a hospital, where a diagnosis of chondrodystrophy was made. He was admitted to the Fernald State School at the age of 9 years because of mental deficiency. He had pneumonia at the age of 11 years, after which he was not able to walk for several months. He had scarlet fever at the age of 12 years, without complications.

Mental Status.—The mental level of this imbecile boy was distinctly lower than that of his sister. He talked in single words and the stunted, short sentences of a 2 year old child. He was unable to hold even a rudimentary conversation.

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21. Determinations of the androgen and estrogen content of the urine were made by Drs. Rinkel and Neustadt at the Research Laboratory, Boston State Hospital.

He could not dress himself and required supervision in his toilet needs. More open, good-natured and responsive than his sister, he always shouted "hello" to whoever entered the ward, smiled readily, responded to marks of affection or approval with manifest pleasure and sought attention of others. He was distinctly more gregarious than his sister and did not discriminate between strangers and

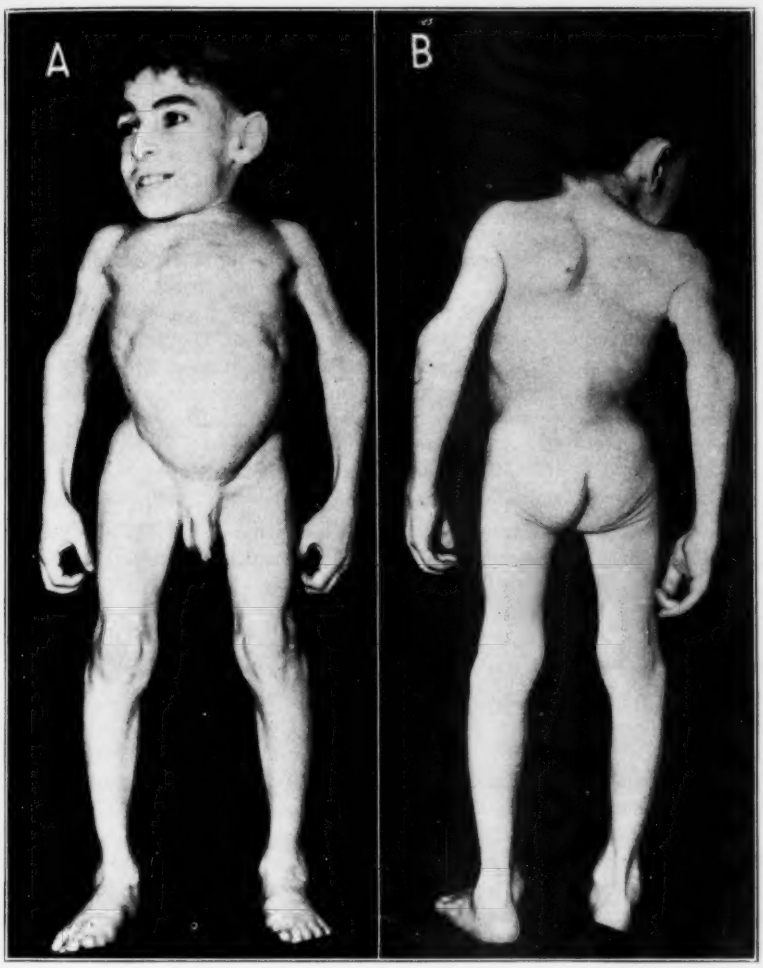

Fig. 2—E. H. (case 2).

the persons of his entourage. He was fond of the radio but showed little interest in picture books. The span of his attention was short. He was exceedingly distractible and restless and was unable to keep still or to carry out requested movements beyond the elementary acts, such as sitting down, getting up or walking.

Physical Status.—The patient was a typical dwarf. His height was 36 inches (91.5 cm.) and his weight 30 pounds (13.6 Kg.), the average normal height for

his age being 58 inches (147.3 cm.) and the average normal weight 98 pounds (44.5 Kg.). Since the age of 9 years his weight had remained unchanged and he had gained only 1.1 inch (2.8 cm.) in height. The circumference of his head was 19 inches (48.3 cm.), which was about 2 inches (5 cm.) under the average. His hair was dark and of normal texture. He had heavy eyebrows and long, dark eyelashes. The nose, throat and teeth were normal. The neck was short, and the chin rested on the sternum. The thyroid was not palpable. There were beading of the ribs and some protrusion of the sternum. The heart and lungs were normal; the blood pressure was 88 systolic and 60 diastolic. The abdomen was protuberant. The liver and spleen were not enlarged. No pubic hair was present; otherwise the genitalia appeared normal. The inguinal glands were enlarged.

In contrast to his sister, he had marked kyphosis, involving the twelfth dorsal and first lumbar vertebrae, with reduction of mobility of the vertebral column but no redness, pain or swelling. Otherwise, he presented skeletal deformities similar to those of his sister. His neck and trunk were short. The head appeared to rest on the thorax. The extremities contrasted with the shortness of the trunk by their normal length. When he was standing with the arms down, the fingers reached the knees. The hip joints had an increased range of mobility. Pes planum was present bilaterally. The gait was typically waddling. The muscles were hypoplastic, lax and weak. Tendon and plantar reflexes showed no abnormalities. There were no cerebellar signs and no incoordination. The insecurity and clumsiness of gait were attributable to the muscular weakness and skeletal deformities. The cranial nerves were intact. The eye movements were free. The corneas were clear and the pupils normal. The fundi showed relative lack of pigment but otherwise were normal. Visual acuity was estimated to be at least 20/50 in both eyes.

Laboratory Studies.—Urine: There was no sugar, albumin or casts; the androgens measured 59 and the estrogens 2,250 international units per day.

Blood: The erythrocytes numbered 4,870,000 and the leukocytes 10,000 per cubic millimeter, with a hemoglobin content of 80 per cent. Calcium measured 8.8 mg., phosphorus 3.5 mg. and cholesterol 146 mg. per hundred cubic centimeters. The Hinton test of the blood for syphilis gave negative results.

Roentgenographic Examination of J. H. and E. H.—The following interpretation of the roentgenographic plates was given by Dr. Edwin Vogt, consulting roentgenologist.

The roentgenographic features in these 2 cases were identical except for the differences attributable to age. The roentgenograms revealed characteristic osteochrondrodysplastic changes. The head was rather large as compared with the body stature but small in relation to the size of the jaws. The hands and feet were short, stubby and spade shaped. The carpal and tarsal bones were irregular and distorted in contour. All the vertebrae were present. They were narrow, and the surfaces of the intervertebral disks were very irregular, a deformity which explains the foreshortening of the trunk. The ribs were wide, especially anteriorly. The epiphysial margins of the scapulas and of the pelvis were stippled and undeveloped. The heads of the femurs and humeri were greatly retarded, and in addition to bilateral coxa vara, there was subluxation of the heads of both femurs. The bones of the extremities, such as the femurs, tibias and humeri, were disproportionately long as compared with the height of the trunk. The epiphyses of the knees were large, resembling the ends of a dumb-bell. The shafts, especially of the femurs, were slender.

It was impossible to obtain satisfactory roentgenograms of the cranial base in our cases, in spite of several attempts.

COMMENT

The condition in our patients must be differentiated from gargoylism, or Hurler's syndrome. In the latter condition the mental deficiency, usually of a severe degree, is associated with dwarfism and skeletal deformities not unlike those seen in Morquio's disease. However, gargoylism is characterized by cloudy corneas, enlarged spleen and liver, large misshaped head and hypertelorism. All these features were lacking in our patients. The clinically manifest skeletal deformities and the results of roentgenographic examinations shown by our patients were sufficiently characteristic to justify classifying the abnormality with Morquio's familial osteodystrophy. The relatively small head, the normal length of the extremities and the pronounced shortening of the trunk readily distinguished these patients from achondroplastic dwarfs, who are characterized by normal length of the trunks, short extremities and a large head with a prominent forehead and flattened bridge of the nose, features which are exactly the reverse of those shown by our patients. The gross mental deficiency was a distinctive feature of our 2 cases of Morquio's disease and apparently was lacking, or was not prominent, in cases of this condition thus far reported. Ruggles,[3] in his series of cases described 2 patients who were mentally defective. However, there are reasons to believe that his patients suffered from the Hurler syndrome, for, besides mental deficiency and skeletal deformities, they showed clouding of the corneas, which, as Veasey [22] pointed out, is highly characteristic of the Hurler syndrome and quite foreign to Morquio's disease. In the case reported by Pohl [14] the patient had an intelligence quotient of 65 and was considered mentally defective. However, this patient was able to complete the formal eighth grade of school at the age of 20 and scored 83.9 on the Stanford achievement test. One may, therefore, doubt whether Pohl's patient was mentally defective to a measurable degree, for a person with an intelligence score of 65 hardly can complete eight grades of school work or achieve as high a score in the achievement test as his patient did.

The etiologic factor in Morquio's familial osteodystrophy is unknown. The low blood calcium level of 5 mg. reported by Morquio was not confirmed by other observers. However, some of the patients had a calcium value of 8 mg., and practically all have been treated with calcium and vitamin D, as well as various endocrine preparations, without results. Consanguinity, emphasized by Morquio as a possible etiologic factor, was present also in our cases. Freeman,[12] Davis and Currier [8] and Jacobsen [16] expressed the belief that Morquio's disease was related to achondroplasia and classified it as an osteochondrodys-

22. Veasey, C. A., Jr.: Ocular Findings Associated with Dysostosis Multiplex and Morquio's Disease, Arch. Ophth. **25**:557-563 (April) 1941.

trophy. Warkany and Mitchell [23] reported a case which they considered as representing a transition between the classic chondrodystrophy of Parrot and the osseous dystrophy of Morquio. They suggested that the two conditions had a common basis. Einhorn and his associates [19] called attention to the possible role of platybasia in the pathogenesis of the condition. Clinically, our patients did not show neurologic abnormalities, so common in persons with platybasia at their age. Giraud and Bert [10] stated that the syndrome was due to an excessive laxity of the ligaments. Morquio [1] suggested the possibility of an endocrine disorder. Up to the present there is no evidence to support this view. Our patients were late in reaching sexual maturity. However, the androgen and estrogen determinations showed that when sexual maturity was established the hormone values were found to be at about a normal level, as in our first patient (J. H.). The low androgen values of her brother (E. H.) could be accounted for by his dwarfism and by his delay in sexual maturation.

SUMMARY

Two cases of familial generalized osseous dystrophy are described. In addition to the skeletal deformities and hypocalcemia originally described by Morquio, a gross mental deficiency was also present. The parents were first cousins. Determination of androgen and estrogen showed normal values in the sister, who reached sexual maturity, and low values in the brother, who is sexually still immature.

The literature is briefly reviewed.

United States Army Medical Corps, Washington, D. C.

United States Army Medical Corps, Camp Edwards, Falmouth, Mass.

Walter E. Fernald State School.

23. Warkany, J., and Mitchell, A. G.: Atypical Chondrodystrophy, J. Pediat. **4**:734-745 (June) 1934.

SURGICAL REMOVAL OF BRAIN ABSCESS DUE TO BACILLUS TYPHOSUS FOLLOWING TYPHOID FEVER

GUY L. ODOM, M.D.
AND
ARTHUR R. ELVIDGE, M.D.
MONTREAL, CANADA

Cerebral complications following typhoid fever are rare, and although cases of meningitis, hemorrhage, thrombosis, embolism, encephalitis and psychosis are reported in the literature, only 1 case of abscess of the brain proved to be due to Bacillus typhosus was discovered at autopsy. For this reason the following case is reported.

REPORT OF A CASE

History.—F. L., a French Canadian aged 21, was admitted to the Montreal Neurological Institute on April 9, 1941, with the complaints of headache, nausea and vomiting for four months and visual failure and aphasia for three months. He had been in good health until August 1940, when he was admitted to the Hôtel-Dieu in a semiconscious state. The diagnosis of typhoid fever was established at this time. He was discharged on November 14, and shortly after returning home began to complain of generalized headache, which gradually increased in severity. About this time he became aware of difficulty in naming objects, although he could recognize them. In January 1941 he noticed that his vision was failing, and this gradually progressed until his admission here.

Examination.—Neurologic examination revealed bilateral papilledema, anomia, alexia and relative accentuation of the right ankle jerk.

Simple roentgenograms of the skull showed no evidence of increased intracranial pressure. A ventriculogram, made on April 16, showed displacement of the third ventricle and the septum pellucidum 1.8 cm. to the right of the midline, elevation and compression of the temporal horn of the left lateral ventricle and some depression of the ventricle as it passed beneath the falx.

Operation.—Immediately after the ventriculographic test a left parietotemporal osteoplastic craniotomy was performed by one of us (A. R. E.). The pressure in the brain was high. The dura was adherent to the pia-arachnoid over an irregular area of about 2 square inches (13 sq. cm.) in the upper temporal region. The flattened cortical surface of the temporal lobe was discolored over a large area extending from the fissure of Sylvius to the base. The fissure of Sylvius was obviously raised by a large mass in the temporal lobe.

By means of blunt dissection, a dark, grayish brown mass, measuring 7 by 5 by 4 cm. and weighing 70 Gm., was removed from the central portion of the left

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

temporal lobe. It extended from the surface almost to the midline and from the fissure of Sylvius down to the base of the middle fossa. The mass bore the general appearance of an extensive malignant growth. After this was removed, a peculiar cyst, 4 cm. in diameter, approximately the size of a golf ball, and weighing 16 Gm., appeared partially embedded in the remaining anterior third of the temporal lobe. The cyst had a smooth, thin, light yellow wall, and on palpation appeared to be filled with some kind of fluid. It was gently separated from the brain and finally delivered without rupture (figure).

Pathologic Studies.—Section of the large mass revealed that it contained at its center 30 cc. of thick yellowish exudate. The following pathologic report was received from Dr. Hugh Starkey, of the department of bacteriology, Royal Victoria Hospital: "Pus on smear showed mostly pus cells, with some well formed poly-

Cyst being removed by blunt dissection.

morphonuclear leukocytes and gram-negative rods. Culture yielded a pure heavy growth of B. typhosus." The second mass (cyst) was filled with clear, straw-colored fluid, which did not yield any organisms on smear or culture.

Examinations of the blood were reported as follows: "B. typhosus H antigen agglutinated the serum nearly completely up to a dilution of 1:640; B. typhosus O antigen, nearly completely up to a dilution of 1:320; Bacillus paratyphosus A H antigen, nearly completely up to a dilution of 1:160, and B. paratyphosus B H antigen, nearly completely up to a dilution of 1:80." Dr. Starkey expressed the opinion that the agglutinations were typical of those obtained after vaccination except for the relatively high titer against B. typhosus O antigen.

Cultures of the cerebrospinal fluid were sterile, and examinations of the stool did not reveal any typhoid bacilli.

Course.—The patient had an uneventful postoperative course, during which his aphasia gradually disappeared and his temperature never rose over 101.4 F. He was discharged on the twentieth postoperative day, when he was free of headache and results of his neurologic examination were relatively normal.

REVIEW OF LITERATURE

Most authors have concluded that abscess of the brain following typhoid fever is due to secondary infection. Keen [1] (1898) collected from the literature references to 4 cases of brain abscess following typhoid fever: those of Deschamps, 1884; Huchard and Tissier, 1885; Hölscher, 1891; Josserand, 1894, and possibly Richardson, 1897. In all these cases abscess was discovered at autopsy, and, unfortunately, in none of them was bacteriologic examination made. Keen [1] added a case described by Terrillon, in 1889, of "presumed osteomyelitis and abscess of the brain following typhoid fever." The abscess was drained surgically, but no bacteriologic or postmortem examination was made.

Prior to this, hemiplegia and aphasia occurring in the course of typhoid fever were generally considered to be due to thrombosis. At this early date Keen suggested, "When a hemiplegia or a monoplegia occurs, while it may be due to thrombosis, it should also raise the question of the possibility of abscess." He further stated that in every case so far reported the outcome had been fatal but that in the future an attempt at surgical intervention might prove successful in such cases.

Brown [2] (1900) reported a case of brain abscess occurring during typhoid fever, with operation and recovery, but the organism cultured from the abscess was Staphylococcus pyogenes aureus. McClintock [3] (1902) was the first to report the occurrence of an abscess of the brain in a case of typhoid fever in which B. typhosus was proved to be the etiologic factor. Cultures were taken at autopsy from the encapsulated abscess and from the meninges over the cerebellum. Scott and Johnston [4] (1915) reported encountering post mortem an abscess of the brain in a case of paratyphoid B, but no organisms were isolated because the brain was immediately fixed in a solution of formaldehyde. Peroni [5] (1931) reported a case of brain abscess and meningitis due to B. typhosus, which he concluded had developed from chronic otitis media. Gram-negative rods (B. typhosus) were found on culture of the cerebrospinal fluid both before and after death. The abscess was discovered at autopsy, but apparently no cultures were made. Postmortem examination did not reveal any other evidence of typhoid fever, and there was no history of the disease.

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1. Keen, W. W.: The Surgical Complications and Sequels of Typhoid Fever, Philadelphia, W. B. Saunders Company, 1898.

2. Brown, A. C.: Jacksonian Epilepsy Due to Cerebral Abscess Following upon Typhoid Fever, Edinburgh M. J. **8**:228-236, 1900.

3. McClintock, R. W.: Brain Abscess in Typhoid Fever Due to Bacillus Typhosus, Am. J. M. Sc. **123**:595-603, 1902.

4. Scott, R. L., and Johnston, W. H.: Brain Abscess in Case of Paratyphoid B, J. Roy. Army M. Corps **26**:444-446, 1915.

5. Peroni, A.: Ototifo cronico con ascesso cerebrale e meningite, Arch. ital. di otol. **42**:500-511, 1931.

COMMENT

The history in this case emphasizes the importance of considering carefully the history in every instance. One should, of course, have in mind cerebral abscess as a possibility when dealing with a rapidly expanding intracranial lesion. Malignant gliomas (glioblastoma multiforme) of this region, although they do occur in this patient's age group, are generally encountered in the fourth, fifth and sixth decades of life. In this case, in spite of the history of typhoid fever, a bone flap was turned. Fortunately, the lesion presented on the surface, and a needle specimen was not taken for biopsy, which would have been extremely dangerous in this case. The lesion was undoubtedly metastatic and of several months' duration, so that the extracapsular method of total removal turned out to be the method of choice in this instance. In cases of tumor it has been the operator's custom to employ an extraneoplastic form of removal whenever possible. This produces the least amount of hemorrhage, helps to delimit the tumor at the start and saves time, trimming being done later as necessary in the case of an infiltrating tumor. In this instance, fortunately, it was the method employed. The pia mater was incised, and a line of separation noted between the brain and the mass with its overlying portion of adherent dura. While considering the advisability of biopsy, separation was continued until the enormous mass of tissue, which looked like a neoplasm of unusual appearance, for example, sarcoma, and, unknown to us, contained the abscess at its center, was finally extirpated, followed by removal of the smaller cyst. To quote from the operative summary:

> The operation turned out to be a complete extracapsular removal of two abscesses (one now known to be a sterile cyst) of the left temporal lobe following typhoid infection. In this case nothing was lost by extracapsular removal without biopsy of what, ordinarily, might well have been mistaken for an inoperable neoplasm in the speech center. The age of the patient made one less willing to believe that the mass might be a glioblastoma multiforme and more inclined to radical removal.

SUMMARY

The clinical history of a patient is presented who, four months after an attack of typhoid fever, was operated on for an expanding intracranial lesion in the left temporal lobe, which proved to be a cerebral abscess from which a pure culture of B. typhosus was obtained. The patient was discharged on the twentieth postoperative day, at which time neurologic examination revealed nothing abnormal. So far as we are aware, this is the first case of brain abscess proved to be due to B. typhosus which followed typhoid fever and was discovered before death, and is, consequently, the first we know of in which the neurosurgical cure was effective.

3801 University Street.

3801 University Street.

APRAXIA

REPORT OF A CASE, WITH AUTOPSY

HARRY A. TEITELBAUM, M.D.

ORTHELLO R. LANGWORTHY, M.D.

AND

ARTHUR B. KING, M.D.

BALTIMORE

John Hughlings Jackson [1] observed that certain aphasic patients could not protrude their tongues when requested to do so. They could, however, eat and drink well, and even lick their lips. While Jackson recognized the significance of this disturbance, he did not designate it by any name. The term apraxia was introduced by Leipmann,[2] who made the first intensive studies of this problem. He [3] pointed out that apraxia is a motor disturbance that cannot be explained as due to paresis, ataxia, motor discharges, speech deafness, agnosia, dementia or disturbances in primary sensation. He stressed the fact that only distinct categories of movement are involved. The apractic patient does not make every purposeful movement erroneously, nor are all purposeful movements of the involved limb in abeyance.

Liepmann [3] designated three types of apraxia: limb-kinetic, ideokinetic and ideational. Limb-kinetic apraxia does not exclude the head region. Only skilful movements of simple pattern are disturbed, and they become crude and garbled. In ideokinetic apraxia the simple limb-kinetic patterns are intact. Many movements can be carried out under certain conditions, but not when the patient wants to execute them. The patient interchanges movements, shifts them to other parts of the body, produces amorphous movements and even omits certain parts; for example, when asked to show his tongue, a patient threw his head back, turned his eyes

From the Subdepartment of Neurology, the Johns Hopkins University, and the Medical Service of the Baltimore City Hospitals.

1. Jackson, J. H.: Remarks on Non-Protrusion of the Tongue in Some Cases of Aphasia, in Taylor, J.; Holmes, G., and Walshe, F. M. R.: Selected Writings of John Hughlings Jackson, London, Hodder & Stoughton, 1932, vol. 2, pp. 146-152.

2. Liepmann, H.: (*a*) Das Krankheitsbild der Apraxia ("motorischen Asymbolie") auf Grund eines Falles von einseitigen Apraxie, Monatschr. f. Psychiat. u. Neurol. **8**:15-44, 102-132 and 182-197, 1900; (*b*) Der weitere Krankheitsverlauf bei dem enseitig Apraktischen und der Gehirnbefund auf Grund von Serienschnitten, ibid. **17**:289-311, 1905; (*c*) Der weitere Krankheitsverlauf bei dem einseitig Apraktischen und der Gehirnbefund auf Grund von Serienschnitten, ibid. **19**:217-243, 1906.

3. Liepmann, H.: Apraxia, Ergebn. d. ges. Med. **1**:516-543, 1920.

up, opened his mouth and made a snapping movement. In ideational apraxia the limb responds obediently but insufficiently. Either there is a delay or parts of the act are omitted or anticipated. Correct movements may be applied to the wrong object. Each portion of the act may be properly performed, but the sequence is disturbed. These three types of apraxia do not as a rule occur in pure and isolated form.

Pick [4] reported a case of ideational apraxia with extensive damage to the brain. Kleist [5] discussed the psychologic mechanisms involved in apraxia in great detail, as did Goldstein,[6] who expressed the belief that lesions of the left frontal lobe were essential for apraxia. Liepmann,[7] however, stressed the defects observed in the corpus callosum and the left supramarginal gyrus in cases of apraxia. Involvement of the corpus callosum has been confirmed by Bonhoeffer [8] and by Ives.[9] Surgical section of the corpus callosum does not produce lasting apraxia, according to Nielsen [10] and Akelaitis.[11] Focal lesions of the supramarginal gyrus (not unlike those in the case to be reported) have been described by von Bechterew,[12] Fearnsides [13] and Bailey.[14] Schaffer [15] and Bonhoeffer,[16] however, observed cases of bilateral destruction of the supramarginal gyri without apraxia.

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4. Pick, A.: Ueber einen eiteren Symptomkomplex in Rahmen der Dementia senilis, bedingt durch starkere Hirnatrophie, Monatschr. f. Psychiat. u. Neurol. **19**:97-108, 1906.

5. Kleist, K.: Ueber Apraxie, Monatschr. f. Psychiat. u. Neurol. **19**:269-290, 1906.

6. Goldstein, K.: Zur Lehre von der motorischen Apraxie, J. f. Psychol. u. Neurol. **11**:169-187 and 270-283, 1908.

7. Liepmann (footnote 2 *b* and *c*).

8. Bonhoeffer, K.: Klinischer und anatomischer Befund zur Lehre von der Apraxie und der "motorischen Sprachbahn," Monatschr. f. Psychiat. u. Neurol. **35**:113-128, 1914.

9. Ives, E. R.: Two Cases of Apraxia with Autopsy, Bull. Los Angeles Neurol. Soc. **6**:46-48, 1941.

10. Nielsen, J. M.: The Unsolved Problems of Apraxia and Some Solutions, Bull. Los Angeles Neurol. Soc. **6**:1-20, 1941.

11. Akelaitis, A. J. E.: Psychobiological Studies Following Section of the Corpus Callosum, Am. J. Psychiat. **97**:1147-1155, 1941.

12. von Bechterew, W.: Ueber die Lokalisation der motorischen Apraxie, Monatschr. f. Psychiat. u. Neurol. **25**:42-51, 1909.

13. Fearnsides, E. G.: A Case of Motor Dispraxia and Paraphasia: Autopsy; Tumour in Supramarginal Convolution, Brain **37**:418-432, 1914-1915.

14. Bailey, P.: A Contribution to the Study of Aphasia and Apraxia, Arch. Neurol. & Psychiat. **11**:501-529 (May) 1924.

15. Schaffer, K.: Ueber doppelseitige Erweichung des Gyrus supramarginalis, Monatschr. f. Psychiat. u. Neurol. **27**:53-74, 1910.

16. Bonhoeffer, K.: Doppelseitige symmetrische Schläfen- und Parietallappenherde als Ursache vollständiger dauernder Worttaubheit bei erhaltener Tonskala, verbunden mit taktiler und optischer Agnosie, Monatschr. f. Psychiat. u. Neurol. **37**:17-38, 1915.

Sittig's [17] monograph on apraxia presents an excellent discussion of the various aspects of this problem. Bertha and Kolmer [18] described an interesting case of apraxia of the facial and speech musculature.

REPORT OF CASE

Mixed aphasia and apraxia. Terminal convulsions of left arm.

J. R., a Negro aged 67, was admitted on Oct. 3, 1940 to Baltimore City Hospitals with the complaint of weakness of the right arm. He could answer only a few simple questions, and speech was incoherent.

General examination revealed a blood pressure of 155 systolic and 80 diastolic, arcus senilis, diminution of hearing, perforation of the nasal septum, large lipoma in the right side of the neck and the left interscapular region and slight enlargement of the prostate.

Neurologic Examination.—The retinal vessels were sclerotic; the peripheral visual fields were normal, and there were no abnormalities of the pupils or the extraocular muscles. Mild weakness of the right lower portion of the face was present, and the right shoulder had limited motility. Study of the motor status revealed slight weakness of the right arm and severe weakness of the leg. Fine movements could not be performed with the right arm. Voluntary movements were athetoid in character. There was slight spasticity in the right leg but none in the right arm. A doubtful grasp reflex was elicited on the right side. The left side was normal. Sensory examination showed that touch and temperature sensations were normal, with probable slight diminution of pain sense in the right leg. Vibratory perception was lost below the pelvis on the right side and below the knee on the left side. Two point discrimination and stereognosis were lost in the right hand. The triceps and radial reflexes in the arms were diminished and equal on the two sides, and while the left biceps reflex also decreased, the right was normal. The abdominal reflexes were absent, as were the ankle jerks. The knee jerks were active and equal on the two sides. There was no clonus, and the Hoffmann reflex was not obtained. Plantar stimulation elicited dorsal flexion of the large toe bilaterally. A confirmatory Oppenheim reflex was also present on each side.

The patient had difficulty in finding words and often used them incorrectly. He could read letters but could not write, even before his illness.

The original impression was that of thrombosis of the left anterior cerebral artery, but that opinion was changed when it was appreciated that there was apraxia of both arms.

Studies on Apraxia.—In response to verbal requests the patient was able to carry out many acts, such as making a fist, showing his teeth or tongue or pointing to his nose. However, when asked to snap his fingers he opened and closed his fist with either hand, and when asked to clap hands he clapped his fist into his palm, alternating hands irregularly. When asked to point to his eye he pointed to his left ear with his left hand and held his right fist against his face and moved his fingers. When requested to throw a kiss he put his right hand to his neck instead of his mouth, and on another occasion he held his right hand out in front of him and made a kissing sound with his mouth without bringing his hand

17. Sittig, O.: Ueber Apraxie, Berlin, S. Karger, 1931.

18. Bertha, H., and Kolmer, H.: Ueber einen Fall von isolierter Apraxie der Gesichts- und Sprachmusculatur, Deutsche Ztschr. f. Nervenh. **146**:102-120, 1938.

to his mouth at all. He could, however, brush his sleeve well with either hand and button his coat with his left hand, but with his right hand he made aimless movements.

In imitation of the examiner he could snap his fingers, but clapped his hands as previously described. Instead of pointing to his nose, he put his left palm over his nose and his right fist to his right cheek. Instead of waving good-by he opened and closed his fists.

When given a comb he named it correctly but used it backward with his left hand. He had difficulty in grasping it with his right hand, but finally succeeded in holding it in his fist and rubbed it on his head. He named a whisk broom correctly and used it properly with his left hand, but when using his right hand he put the brush in his lap and rubbed himself with his hand. He later used it correctly. When given a cigaret and a box of matches he put the cigaret in his mouth with his left hand, then opened the box and tried to get a match out but could not. Finally, he took one out with his left hand, but he rubbed his right thumb on the box as though trying to light it. After considerable manipulating, during which he dropped objects, he succeeded in striking a match on the box. He almost burned his fingers, but he made no effort to avoid the fire, which had to be blown out by the examiner.

Laboratory Studies.—The Eagle test of the blood for syphilis showed a positive reaction. The spinal fluid was anticomplementary for syphilis. The colloidal gold curve was 555431100. The urine was normal. A blood count revealed 3,400,000 red cells and 8,200 white cells per cubic millimeter and 80 per cent hemoglobin.

Course.—On December 31 the patient suddenly lost consciousness and had clonic spasms of the left arm. His head and eyes were turned to the right. Cervical rigidity was pronounced. The temperature rose to 104.6 F. on January 1, 1941, and respiration ceased.

General Postmortem Observations.—There were extensive consolidation of the lower lobe of the left lung, due to pneumonia and atelectasis; confluent lobular pneumonia of the right lung, and syphilitic aortitis.

Brain.—Gross Examination: The vessels making up the circle of Willis were soft and patent. There was, however, a firm thrombus in the left middle cerebral artery as it lay in the first part of the sylvian fissure. A softer thrombus was present in the first portion of the left anterior cerebral artery, while both anterior cerebral arteries were thrombosed as they passed over the genu of the corpus callosum. The ventricles were not enlarged.

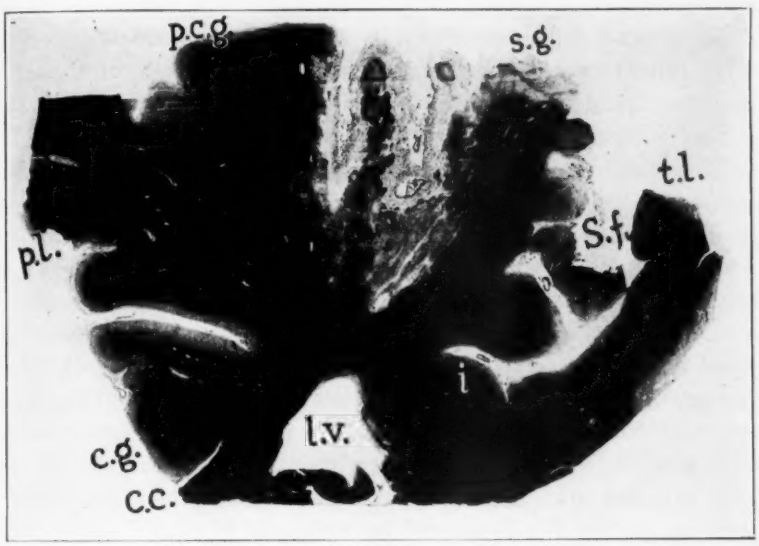
The meninges over the convexity of the cerebrum were infiltrated with small yellow-white plaques, which were confluent in some places. This infiltration extended only about 1 inch (2.5 cm.) parasagittally from the midline.

There was a circumscribed area of cerebral atrophy due to softening in the left inferior parietal lobule, in which region the arachnoid and pia were adherent. The ventral border of the soft area extended to the sylvian fissure, involving the posterior part of the postcentral gyrus and the anterior part of the supramarginal gyrus to an extent of 2 cm. The lesion extended dorsally for 4.5 cm. and at its dorsal end was 1.5 cm. wide. In the ventral 3 cm. of the lesion only the posterior border of the postcentral gyrus was involved, while in the more dorsal 1.5 cm. the entire postcentral gyrus was soft.

The right frontal pole showed evidence of recent softening on its medial surface and lateral convexity. The right side of the genu of the corpus callosum was similarly involved. There was a like degree of softening on the medial aspect of the left frontal lobe.

Microscopic Study: A section through the left parietal lobe (figure) at the junction of the postcentral and the supramarginal gyrus showed a large area of degeneration extending outward from the corpus callosum and including the cortex. The fibers of the insula were spared. The cortex was extremely shrunken in this area. The deeper parts of the white matter in this lesion were porous. Hematoxylin and eosin stains showed that the adjacent cortex was normal. There was a small area of softening in the tip of the insula, involving the cortex only.

A section through the left frontal lobe caudal to the tip of the anterior horn of the lateral ventricle showed an area of partial demyelination just lateral to the anterior horn. This was the region of the superior occipitofrontal fasciculus. Anterior and medial to the floor of the ventricle was an area of softening that cut off the lower fibers of the corpus callosum.



Frontal section through the left cerebral hemisphere at the junction of the postcentral and the supramarginal gyrus, showing area of atrophy. Here, *c.c.* indicates corpus callosum; *l.v.*, lateral ventricle; *p.l.*, paracentral lobule; *i.*, insula; *c.g.*, cingulate gyrus; *p.c.g.*, postcentral gyrus; *S.f.*, sylvian fissure, and *s.g.*, supramarginal gyrus.

Myelin-stained sections of the right frontal lobe at the anterior tip of the lateral ventricle showed only slight variations in the intesity of stain. In hematoxylin and eosin preparations the gray matter above the middle frontal sulcus was very porous, and a certain amount of porosity was also present in other parts of the cortex.

A section through the basal ganglia, the corpus callosum and the third ventricle showed well myelinated fibers in the internal capsule, the basal ganglia, the optic tract, the fimbria and the corpus callosum.

The medulla showed pigmentary atrophy of cells and amyloid infiltrations.

The left middle cerebral artery showed an organized clot, with splitting of the internal elastic membrane. There was no canalization.

COMMENT

The patient showed no apraxia of the head region. Simple movements, such as making a fist and spreading the fingers, were executed well in most instances, but on imitation of a fist with his left hand he opened and closed his hand, indicating that limb-kinetic apraxia was present to some degree. The more complex movements were carried out poorly, though not constantly so. He failed with his right hand in pointing to his eye and in throwing a kiss, and with his left hand in waving good-by, catching a fly and grinding coffee. In some instances he failed with both hands, as in saluting and waving good-by and pointing to his eye in imitation. These deficiencies showed that the predominant disturbance present was of the ideokinetic type. The patient had considerable difficulty in lighting a cigaret, as previously described. During some of the tests he left out steps in the procedure, though he seemed to have the general idea. This type of performance could be classified as ideational apraxia.

The occurrence of the three types of apraxia in the same case is in conformity with Liepmann's [3] observation. The lesions of significance were those in the left supramarginal gyrus and in the left frontal lobe, involving the fibers of the corpus callosum. These observations agree with those reported by other investigators, as already mentioned. The bilateral disturbances were due to the fact that the left cerebral hemisphere is dominant in right-handed people with regard to apraxia, as well as aphasia. The ability to perform complex purposeful movements, which will be referred to as eupraxia, depends on the adequate government of the motor centers of the cerebral cortex by the properly integrated functions of certain vital cortical areas and association pathways located in the dominant cerebral hemisphere. If enough of this vital cerebral tissue is destroyed, bilateral apraxia results, as in the case described, inasmuch as both motor centers are deprived of its influence. The pathway through which the dominant left cortex controls the motor center of the right cerebral hemisphere passes through the corpus callosum. Destruction of these callosal fibers alone would isolate only the right motor center from the left cortical areas essential for eupraxia, and apraxia of the left side would result. Isolation of the left motor center from the areas of the dominant left cortex essential for eupraxia, with sparing of these areas as well as of the callosal fibers just described, would cause apraxia of the right side. The early softening in the right frontal lobe in the present case must have been a terminal event, causing the clonic convulsions in the left arm just before death.

The fact that apraxia does result from focal lesions in certain parts of the brain is not evidence for the existence of a center governing com-

plex purposeful movements. Eupraxia, Liepmann [19] stated, depends on the proper association of the motor center with many areas of the brain. Lesions of these areas, especially those involving their connections with the motor centers, can cause apraxia. The most vulnerable areas are the parietal lobe just posterior to the central gyri, the central gyri with their associated white matter and the corpus callosum. It is generally agreed, however, that ideational apraxia results from diffuse cerebral destruction. Nielsen [10] came to conclusions not unlike those of Liepmann in that he saw no evidence of a center for eupraxia. Rather, the associated action of various parts of the cerebral cortex forms the basis for purposeful complex movements. Lesions in various sites can prevent such associated action and cause apraxia. Similar mechanisms govern the production of agnosia and aphasia, as indicated by the analysis of Henschen's [20] accumulated data by one of us (H. A. T.).[21]

SUMMARY

A case of bilateral apraxia involving limb-kinetic, ideokinetic and ideational disturbances is described. Postmortem studies of the brain revealed a large lesion involving the left supramarginal and postcentral gyri and smaller lesions in the centrum ovale of the left frontal lobe, including corpus callosum fibers to some degree. The fact that apraxia can be caused by focal lesions, as described in this case, does not justify the conclusion that there is a center for eupraxia. Lesions in various sites can cause apraxia if they destroy essential cortical areas and association pathways. These are particularly vulnerable when the region of the left supramarginal gyrus is impaired in right-handed people.

Johns Hopkins Hospital.

19. Liepmann, H.: Bemerkungen zu v. Monokows Kapitel "Die Lokalisation der Apraxie" in seinem Buch: Die Lokalisation in Grosshirn (1914), Monatschr. f. Psychiat. u. Neurol. **35**:490-516, 1914.

20. Henschen, S. E.: Klinische und anatomische Beiträge zur Pathologie des Gehirns: VI. Ueber sensorische Aphasie, Stockholm, Nordiska Bokhandel, 1920.

21. Teitelbaum, H. A.: The Principle of Primary and Associated Disturbances of the Higher Cortical Functions as Applied to Temporal Lobe Lesions, J. Nerv. & Ment. Dis., to be published.

COMPLETE HEART BLOCK OCCURRING DURING INSULIN SHOCK THERAPY

Report of a Case

A. R. Berger, M.D., and Walter Goldfarb, M.D., New York

In the extensive literature concerning the therapeutic and experimental use of insulin, a great number of electrocardiographic changes have been recorded, including disturbances of cardiac rate and rhythm and alterations in the amplitude or configuration of the various waves in the electrocardiogram. To date, however, we have been unable to find any instance of auriculoventricular dissociation during insulin shock, and the case herein reported is submitted as an instance of such a phenomenon.

REPORT OF CASE

History.—W. V., a white man aged 21, was admitted to the psychiatric department of the Bellevue Hospital on March 5, 1940 with a diagnosis of paranoid schizophrenia. The psychosis was of about eleven months' duration, and the patient was considered to be a suitable candidate for insulin shock therapy. His medical history was irrelevant, and he had never had any manifestations of diminished cardiac reserve.

Examination.—Physical examination on admission revealed a well developed, extremely tall and thin man, who showed no evidence of somatic disease. Specifically, the cardiovascular system and the teleroentgenogram of the heart were normal. The electrocardiogram had inverted T waves in leads II and III but was otherwise not remarkable. It was felt that that these minor changes were compatible with the patient's body build.

Course.—Insulin therapy was started on March 7, 1940, and the dose was progressively increased, since the patient did not go into coma. On April 2 the patient first became comatose, after receiving a dose of 310 units of insulin. Coma was terminated by administration of dextrose by tube, and no apparent change was noted for the rest of the day. On April 3, at 5:30 a. m., the patient was aroused by severe pain experienced substernally and in the right upper part of the chest and complained of a feeling of being "blown up." The pain radiated to the right side of the neck and lasted about twenty minutes. He claimed to have slight difficulty in breathing and some abdominal cramps. There had been no chill or bloody sputum. The pulse was very rapid at first, but the patient soon became pale and weak and the pulse rate dropped to 36 per minute. The systolic blood pressure was 110 mm. and the diastolic pressure 50 mm. of mercury. The heart sounds were normal, and no murmurs were heard.

Reexamination at 8 a. m. revealed that the patient was comfortable and lying flat in bed. Respiration was regular and slow. The rectal temperature was 94 F. The apical impulse of the heart was diffuse in the fifth interspace outside the midclavicular line. The aortic second sound was greater than the pulmonic and neither was accentuated. The pulse rate was equal to the ventricular rate of 38 per minute. A soft systolic murmur was heard at the apex. There were no thrill, diastolic

From the Psychiatric Medical Service and the Department of Psychiatry, Bellevue Hospital.

murmur, gallop or pericardial friction rub. Scattered sibilant rales were heard in both lungs. There were no signs of congestive heart failure.

On April 4 the temperature rose to 100.8 F., and clinical and roentgenologic evidence of consolidation of the upper lobe of the right lung developed. At no time did the patient have a chill, and sputum was never produced. Material from repeated pharyngeal swabbings inoculated into mice failed to yield etiologic organ-

Summary of Electrocardiographic Data in Case of Complete Heart Block

Date	Rhythm *		Conduction	Ventricular Complex	Precordial Leads
	Auricle	Ventricle			
2/9/40	N S R	N S R	Normal	Supraventricular; T_2 and T_3 inverted	
4/3/40 a.m. (fig. 1)	S T	Idioventricular (slightly irregular)	Complete AV block and incomplete left B B B †	Aberrant (QRS of 0.11 sec.); incomplete left B B B	Slight delay in excitation of left ventricle; abnormal R waves in CF_3, CF_4, CF_5 and CF_6
p.m. (fig. 2)	S T	Idioventricular (regular)	Complete AV block and incomplete right B B B	Aberrant (QRS of 0.11 sec.); incomplete right B B B; prominent S_1	Abnormal R waves in CF_1, CF_2 and CF_3; slight delay in right ventricular excitation
4/4/40 p.m. (fig. 3)	S T	S T	Incomplete AV block with occasional Wenckebach phenomenon	Supraventricular; T_1, T_2, T_3 low	Low T waves in CF_4, CF_5 and CF_6
4/5/40 (fig. 4)	N S R	N S R	Incomplete AV block with occasional Wenckebach phenomenon	Supraventricular; T_2, T_3 inverted	Low R waves in CF_3 and CF_4; inverted T waves in CF_5 and CF_6; minimal S-T elevation in CF_3
4/6/40	N S R	N S R	Incomplete AV block with occasional Wenckebach phenomenon	Supraventricular; deep Q_3; T_3 inverted	
4/8/40 (fig. 5)	N S R	N S R	Incomplete AV block (prolonged PR interval)	Supraventricular	
4/10/40	S B	S B	Incomplete AV block (prolonged PR interval)	Supraventricular	
4/12/40	S B	S B	Incomplete AV block (prolonged PR interval)	Supraventricular	
4/15/40	N S R	N S R	Normal	Supraventricular	
4/18/40	N S R	N S R	Normal	Supraventricular; T_3 inverted	
5/17/40	N S R	N S R	Normal	Supraventricular; T_2 diphasic; T_3 inverted	

* N S R indicates normal sinus rhythm; S T, sinus tachycardia, and S B, sinus bradycardia.
† B B B indicates bundle branch block.

isms; blood cultures likewise were sterile. Satisfactory response was made to sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and symptomatic therapy, and the parenchymal lesion subsided completely within four days.

During this interval a cardiac arrhythmia, which clinically simulated dropped beats or premature contractions, persisted. The nature of this rhythmic disturbance is made clear by inspection of the electrocardiograms.

Physical recovery was complete. On April 26 examination of the heart revealed no abnormalities. Fluoroscopy revealed a normal cardiovascular silhouette. There was, however, no change in the psychiatric status, and the patient was discharged to the Rockland State Hospital on May 21, 1940.

Electrocardiograms.—The salient electrocardiographic features are summarized in the accompanying table. A tracing taken in February 1940, with the patient sitting upright, revealed normal sinus rhythm with PR and QRS intervals of 0.14

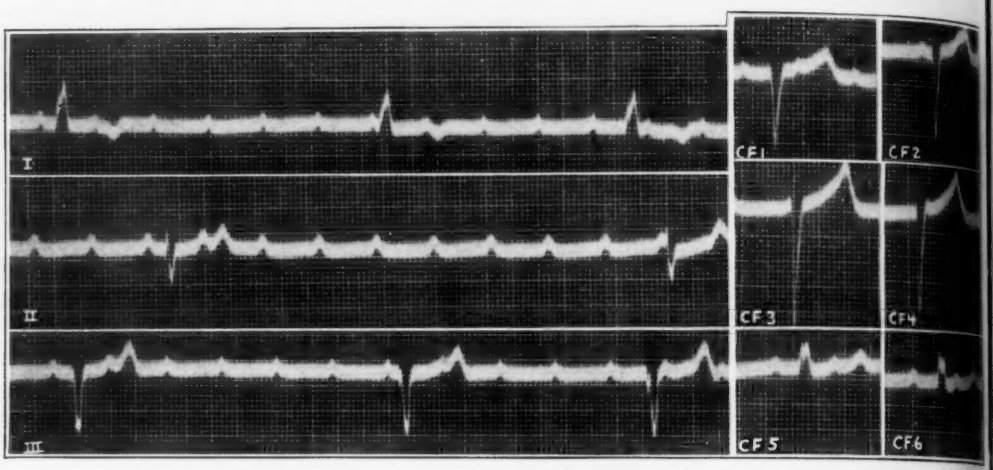


Fig. 1.—Standard electrocardiograms (I, II and III) and precordial leads taken about five hours after onset of symptoms. In this, and in the subsequent illustrations, the standard leads were recorded with the string at normal sensitivity; the precordial leads were recorded at half-normal sensitivity (see text). Precordial leads were taken according to the method suggested by the Joint Committee for the Standardization of Precordial Leads (*Am. Heart J.* **15**:107 and 235, 1938).

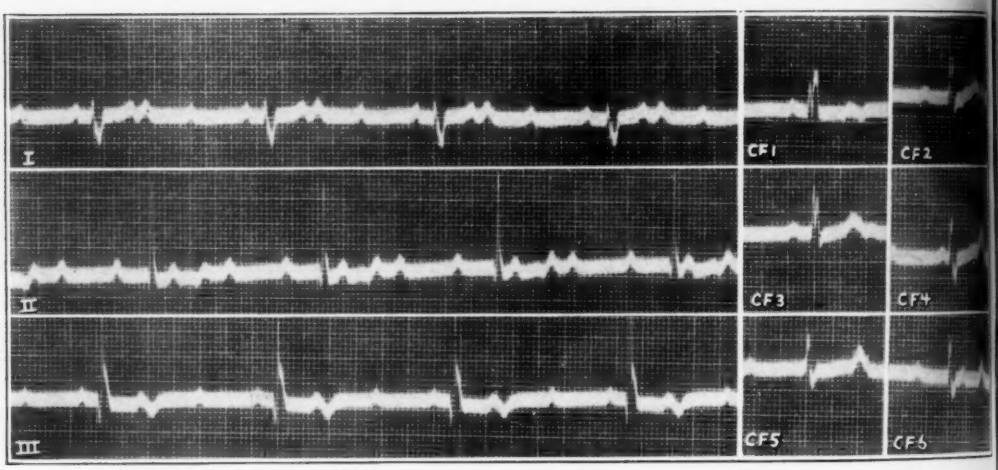


Fig. 2.—Electrocardiograms taken about eleven hours after onset of symptoms (see text).

and 0.07 second, respectively. There was mild right axis deviation, and the Q wave in lead III was prominent, with inversion of the T waves in leads II and III.

The electrocardiographic pattern was considered to be normal for the patient's age and habitus.

The electrocardiogram (fig. 1) taken about five hours after the onset of the acute episode aforedescribed differed significantly from the control tracing. There was

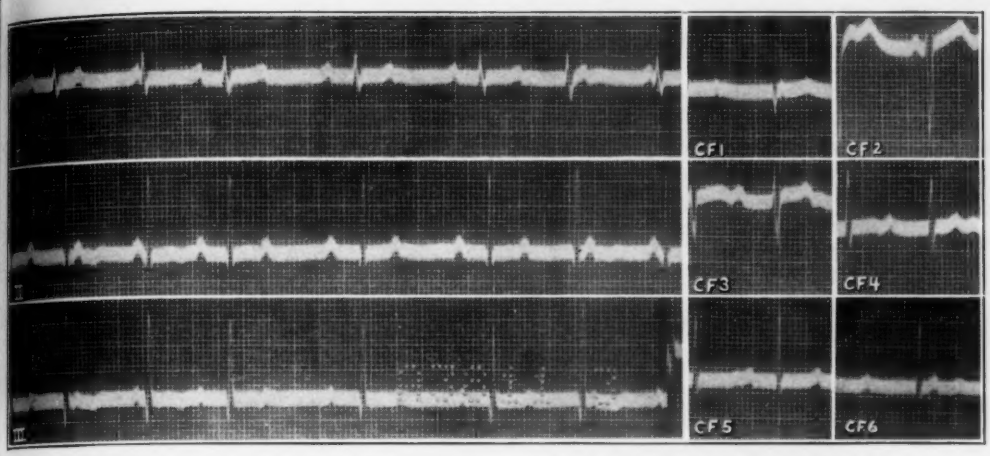


Fig. 3.—Electrocardiograms taken about thirty-five hours after onset of symptoms (see text).

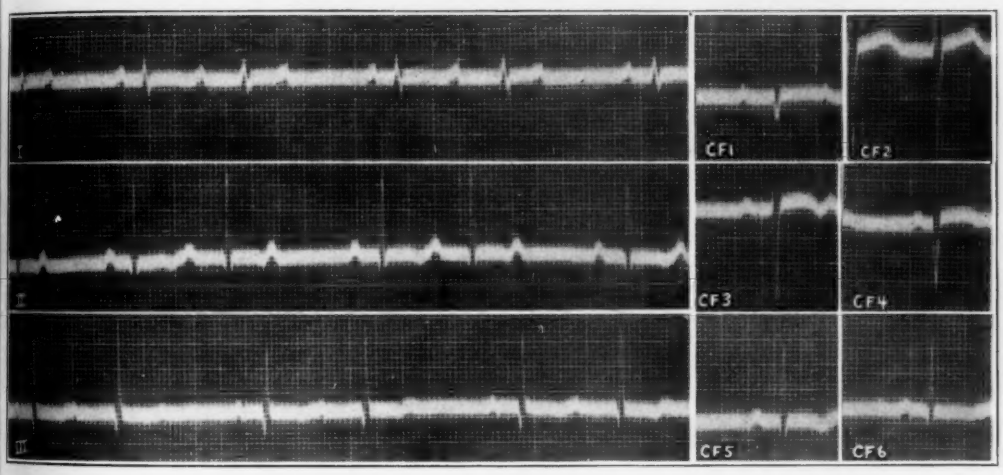


Fig. 4.—Electrocardiograms taken about fifty hours after onset of symptoms (see text).

sinus tachycardia with complete auriculoventricular heart block. The ventricular rhythm, arising in an idioventricular center, was slightly irregular, probably due to occasional exhaustion of the center. The QRS interval was prolonged to 0.11 second, and the complex itself was of the type associated with discordant left bundle branch block. It is impossible to state whether this abnormality was

the result of disturbance in the passage of excitation through the bundle branches or myocardium of a stimulus which originally arose above the bifurcation of the common bundle, or the result of an idioventricular center located somewhere below that bifurcation, as, for example, in the right main bundle branch. The precordial potentials revealed slight delay in the excitation of the left ventricle; the R waves in the third through the sixth point were abnormal.

About eleven hours after the onset of symptoms the electrocardiogram revealed complete heart block (fig. 2). The ventricular complex now was of the type found in cases of incomplete right bundle branch block, with a prominent, slurred S wave in lead I. The precordial potentials were entirely different from those recorded only six hours before, and showed that there was slight delay in right ventricular excitation.

By the following day, thirty-five hours after onset (fig. 3), there was sinus tachycardia with incomplete auriculoventricular block and dropped ventricular beats (Wenckebach phenomenon). The QRS complex was of the supraventricular

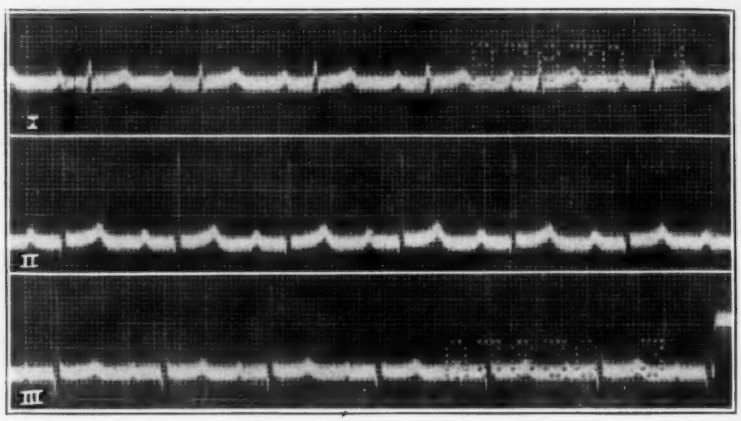


Fig. 5.—Electrocardiograms taken about five days after onset of symptoms.

type, but the final ventricular deflection was low in all limb leads. The precordial derivations showed low T waves in points 4, 5 and 6.

The standard leads of the tracing shown in figure 4 resembled those of the previous day in all respects. In the precordial leads, the R wave was low in points 3 and 4, and there was minimal deviation of the S-T segment in point 3. T waves in points 5 and 6 were inverted. These facts indicated abnormalities in the passage of excitation to the epicardial surface of the heart beneath the exploring electrode, but whether they were due to localized disturbances in the conduction system or to circumscribed areas of myocardial damage we are not prepared to state.

The electrocardiographic abnormalities regressed gradually, and the tracing taken about six weeks after the acute episode resembled in every respect the normal control tracing.

SUMMARY

A case of complete heart block occurring during insulin therapy for schizophrenia is reported.

New York University College of Medicine, Bellevue Hospital.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

NEUROSECRETION: I. THE NUCLEUS PREOPTICUS OF FUNDULUS HETEROCLITUS L. ERNST SCHARRER, J. Comp. Neurol. **74**:81 (Feb.) 1941.

More than 100 brains of Fundulus, a small fish, were fixed in Zenker's fluid to which was added solution of formaldehyde U. S. P. and embedded in pyroxylin. Serial sections were stained with a modification of Masson's trichrome method. The large cells of the nucleus preopticus showed many variations, due to differences in the kind and number of cytoplasmic inclusions, to the vacuolation of the cytoplasm and to changes in the arrangement of the Nissl substance. Usually all the cells of the preoptic nucleus of one specimen showed the same type of structural peculiarities. When the cells appeared to be secreting they were filled with granules and colloid droplets. In some cells were also large vacuoles filled with a substance which stained differently from the colloids. The process of the elaboration of colloid appeared to be followed by a stage of storage and gradual consumption of the product. In the final stage no, or little, colloid was present and the cells showed small vacuoles containing only a little debris, of no particular stainability. Cells which appeared to be inactive were characterized by peripheral localization of coarse Nissl granules, a frequently eccentric position of the nucleus and the occurrence of a polymorphous nucleus. The changes in the appearance of these cells cannot be attributed to nervous functions but are to be considered evidence of a secretory cycle in these temporarily transformed nerve cells.

FRASER, Philadelphia.

THE ANATOMICAL RELATIONSHIPS OF ABNORMALLY LOCATED MAUTHNER'S CELLS IN FUNDULUS EMBRYOS. JANE M. OPPENHEIMER, J. Comp. Neurol. **74**:131 (Feb.) 1941.

Mauthner's cells are giant neurons, normally present in fishes and some tailed amphibians, one on each side of the medulla at the level of the entrance of the eighth cranial nerve. In the study of young fish embryos in which grafting experiments had resulted in the formation of supernumerary Mauthner cells Oppenheimer followed the course of the axons of these cells and made deductions concerning the influences which guide the direction of their growth. The operations were performed toward the end of the first day of development. Portions of the germ ring, which were chiefly presumptive mesoderm, were grafted to the head-forming region of the embryonic shield of gastrulae of the same age as the donors. The grafts differentiated into or induced the formation of additional head structures, such as brain and ear, in the host. In 14 embryos 22 supernumerary Mauthner cells were found. The axons of 21 of these cells could be followed, and 18 were observed to send their fibers into the primary cord. Thirteen of them occupied the usual position in the cord, adjacent to the medial longitudinal fasciculus. Three were found more dorsally in the cord, adjacent to the lateral longitudinal fasciculus. Oppenheimer suggests that the two longitudinal fasciculi, which are very early myelinated in Fundulus, have a directive influence on the growth of the axon of the Mauthner cell.

ADDISON, Philadelphia.

THE PYRAMIDAL TRACT OF THE MONKEY: A BETZ CELL AND PYRAMIDAL TRACT ENUMERATION. ARTHUR MARVEL LASSEK, J. Comp. Neurol. **74**:193 (April) 1941.

The right motor cortex was removed from the brains of 4 mature monkeys. Serial sections were made from the medial surface to the lateral extremity of each motor cortex and the gigantopyramidal, or Betz, cells enumerated. The following criteria were used for typing these large motor cells: They must be situated in the infragranular layer, be large and pyriform, have an abundant Nissl substance with a marked affinity for the stain and possess a spherical nucleus which in most instances is small in proportion to the amount of cytoplasm. Other large cells in the fifth layer of the cortex were included in the counts. The pyramids were treated by the protargol (protein silver) technic to demonstrate the fibers. An average of 18,845 Betz cells was obtained from each of the 4 monkeys. Of the Betz cells in the motor area, 5,905 (31.3 per cent) were buried within the central sulcus and 12,940 were situated on the exposed cortical surface. The cells in the motor cortex were distributed as follows: upper third, 51.9 per cent; middle third, 32.8 per cent, and lower third, 15.3 per cent. In the pyramidal tract just rostral to the motor decussation 554,000 corticospinal fibers were calculated. The fibers were predominantly minute axons. From the evidence it appears that only a small fraction of the fibers in the pyramids of monkeys belong to the Betz cells of area 4.

ADDISON, Philadelphia.

EQUIVALENT LOSSES IN ACCURACY OF RESPONSE AFTER CENTRAL AND AFTER PERIPHERAL SENSE DEPRIVATION. CECILE BOLTON FINLEY, J. Comp. Neurol. **74**:203 (April) 1941.

Rats were trained to run a special type of maze, first in the light and then in the dark. By means of a thermocautery, applied to the exterior surface of the rats' skulls, the striate areas of the cortex were destroyed. The animals were again allowed to run in the maze in the light and in the dark. At the end of the experiment they were killed and the depth and location of the lesion plotted. Comparison of the results of the preoperative and postoperative experiments showed that interference with the central reception of visual cues under the conditions described produced no greater loss of accuracy than did the enucleation of the eyes.

FRASER, Philadelphia.

EFFECTS OF CUTTING THE TROCHLEAR AND ABDUCENS NERVES ON THE END BULBS ABOUT THE CELLS OF THE CORRESPONDING NUCLEI. MELVIN SCHADEWALD, J. Comp. Neurol. **74**:239 (April) 1941.

Schadewald severed the trochlear and abducens nerves of 9 adult cats by removing the contents of the orbit on one side. After three to one hundred days the brains of these animals were treated by the Cajal technic and then sectioned. The number and size of *boutons terminaux* about the cells of the nuclei of the trochlear and abducens nerves on the control side were of the same order as those about the somatic motor cells of the spinal cord, and there was no significant change in size or number of *boutons* about the cells the axons of which had been cut.

ADDISON, Philadelphia.

VASCULARIZATION IN THE BRAINS OF REPTILES: I. THE PAINTED TURTLE, CHRYSEMYS PICTA MARGINATA AGASSIZ. E. HORNE CRAIGIE, J. Comp. Neurol. **74**:247 (April) 1941.

The arterial system of 10 painted turtles was injected through the heart with carmine gelatin. Serial sections of the brain were made and the size and distribution of the capillaries studied. The total length of the capillaries in a unit volume of tissue was measured in twenty-four parts of the brain. In general the brain of the turtle was only slightly better vascularized than that of the frog.

The median longitudinal fasciculus was the most poorly vascularized. The magnocellular portion of the cochlear nucleus had the richest circulation in the brain. The chief sensory nucleus of the fifth nerve and the ventrolateral vestibular nuclei had considerably more abundant vascularization than the motor centers. The average diameter of 50 capillaries measured in different parts of the brains of different specimens was 7.1 microns. The cortex of the cerebellum was less well supplied than its lateral nucleus, which corresponds to the mammalian dentate nucleus.

ADDISON, Philadelphia.

ONE KIND OF RECURRENT FIBERS IN THE CEREBELLAR CORTEX OF THE MONKEY. HSIANG-TUNG CHANG, J. Comp. Neurol. **74**:265 (April) 1941.

In sections of the vermis of the monkey prepared by Bielschowsky's technic many fine, unmyelinated fibers were seen ascending from the granular into the molecular layer to a point near the surface of the cortex and descending by a small loop back to the granular layer. Thus the loop had two parallel limbs running almost perpendicular to the surface of the cortex. Such loops were seen only in sections cut at right angles to the long axis of the folium. The recurrent fibers were more frequently seen in the basal than in the apical portion of the folium. Their origin and destination were not determined.

ADDISON, Philadelphia.

CHEMORECEPTORS IN THE ABDOMEN. W. HENRY HOLLINSHEAD, J. Comp. Neurol. **74**:269 (April) 1941.

Nonchromaffin epithelioid cell groups associated with the vagus nerves in the abdomen were studied in the adult mouse and albino rat after various stains and after silver impregnation. Such bodies were found in more than 100 mice. There was considerable variation in the size, position and number of cell groups but apparently not in the total amount of this tissue present in the adult. The majority of the bodies in the adult mouse measured less than 0.1 mm. in their greatest diameter, though some larger ones were observed. Twenty or more were frequently seen in the same animal in a limited area along a portion of the right vagus nerve. Similar bodies were found in the same location in 4 adult and 6 young rats. Serial sections of the same region from 4 adult cats, 3 young guinea pigs and 4 young rabbits failed to reveal any tissue of this type. The innervation of the abdominal bodies was abundant and arose from the dorsal root ganglia, reaching the abdomen in part through the splanchnic and in part through the vagus nerves. Experiments made on both rats and mice indicate that appropriate stimulation of the abdominal bodies may influence respiration.

ADDISON, Philadelphia.

DEVELOPMENT OF THE TRACTUS SOLITARIUS. EARLE E. WILSON, WILLIAM F. WINDLE and JAMES E. FITZGERALD, J. Comp. Neurol. **74**:287 (April) 1941.

This investigation was concerned with the comparative development of the tractus solitarius in silver-impregnated material of cat, rat, sheep and human embryos. Elements which contribute to the tract were recognized in the cranial ganglia of embryos of cats as small as 5 mm. in length. At the 5 mm. stage fibers from cells in the geniculate, petrosal and nodose ganglia entered the neural tube. In embryos 6 mm. long a continuous tractus solitarius was present in the medulla between the levels of the glossopharyngeal and the vagus nerve. By the 8.5 mm. stage fibers from the facial nerve were seen entering the tract. At the 10 mm. stage the tract received a few fibers from the spinal accessory nerve. In larger cat embryos some of the more caudal fibers of the tract crossed to form a dorsal commissure at the lower end of the medulla. In the rat the tractus solitarius in its early stages of formation was superficially placed in the marginal layer. As the vestibular and trigeminal fibers extended farther down the medulla

in larger embryos the tract became displaced into the mantle layer as far caudad as the hypoglossal nerve. No dorsal commissure was seen in the series of rats studied. In the series of sheep and human embryos the tractus solitarius was similar to that in the cat and rat. There were six modes of termination of the tractus solitarius in the embryos studied. 1. Most of the fibers of the tract ended along its course within the nucleus of the tractus solitarius. 2. Medially streaming fibers terminated in or near the motor nucleus of the facial nerve and among interneurons between the mantle and the ependymal layer rostral to the glossopharyngeal nerve. 3. Some fibers joined the ventrolateral and some the dorsomedial part of the dorsal funiculus of the same side, and others passed into the dorsomedial part of the dorsal funiculus of the opposite side and probably into the primordium of the commissural nucleus. 4. The most caudal fibers of the tractus solitarius terminated and became lost in the mantle layer of the spinal cord between the first and the fifth cervical nerve.

FRASER, Philadelphia.

STUDIES OF THE VERTEBRATE TELENCEPHALON: II. THE NUCLEAR PATTERN OF THE ANTERIOR OLFACTORY NUCLEUS, TUBERCULUM OLFACTORIUM AND THE AMYGDALOID COMPLEX IN ADULT MAN. ELIZABETH CAROLINE CROSBY and TRYPHENA HUMPHREY, J. Comp. Neurol. **74**:309 (April) 1941.

Crosby and Humphrey correlate the finer nuclear configuration of the anterior olfactory nucleus, the tuberculum olfactorium and the amygdaloid complex in adult man with that of the corresponding centers in various mammals. A single series of sections from adult human material stained with toluidine blue forms the basis of the study. A thorough histologic description of the many subdivisions and the various nuclei is given. The anterior olfactory nucleus is a discontinuous series of cell clusters seen in the olfactory bulb, the olfactory crus and the base of the hemisphere. Lack of continuity of these cell masses is probably the result of stretching out of the nucleus by a forward spread of the olfactory formation. There is no cleancut differentiation of a pars externa in the anterior olfactory nucleus in man, and this is probably related to the absence of an accessory olfactory bulb in adult man. Nor does the gray substance making up the various portions of the anterior olfactory nucleus form a complete periventricular ring, as is characteristic of most mammals. The tuberculum olfactorium has three layers, plexiform, pyramidal and polymorphic, comparable to those in other mammals. A typical large island of Calleja is demonstrable in man, as well as smaller islands. All of the amygdaloid nuclei customarily described for mammals are identifiable. Most of these are relatively well developed.

FRASER, Philadelphia.

Physiology and Biochemistry

NUTRITIONAL DERMATOSES IN THE RAT: VII. NOTES ON THE POSTURE, GAIT, AND HYPERTONICITY RESULTING FROM A DIET CONTAINING UNHEATED DRIED EGG WHITE AS THE SOURCE OF PROTEIN. M. SULLIVAN, L. KOLB and J. NICHOLLS, Bull. Johns Hopkins Hosp. **70**:177 (Feb.) 1942.

Sullivan and his co-workers fed rats weighing 30 to 35 Gm. and approximately 18 days of age the following diet: dried commercial egg white, 30 per cent; corn starch, 17.7 per cent; sucrose, 18.5 per cent; McCollum salts no. 51, 5.8 per cent; peanut oil, 15 per cent; cod liver oil, 3 per cent, and a yeast extract equivalent to 10 per cent dry yeast. Within four to eight weeks there developed generalized pruritic, exfoliative dermatitis. At the height of the cutaneous involvement abnormal posture and hypertonicity were usually observed.

Histologic examination of the muscles of the posterior extremities in 16 of the severely affected rats (11 to 31 weeks of age) showed swelling and increase in the number of the sarcolemma cells. In some cases this was so extensive that whole muscle fibers appeared to be destroyed. The signs of egg white injury

were not delayed or modified in a group of 6 rats fed the egg white diet supplemented with alpha tocopherol in doses of 20 mg. orally and 20 mg. subcutaneously two times a week. The question of the etiology of the muscle lesion needs elucidation, particularly in view of the opinion expressed by Eddy and Daldorf that similar lesions are common in apparently unrelated dietary deficiencies.

No anatomic changes were observed in the forebrain, hindbrain, spinal cord, posterior root ganglia or sciatic nerves. As there were no cellular changes in the central nervous system, the muscle alterations were not considered to have been secondary to changes in motor ganglion cells.

It is suggested that the hypertonicity may be due to irritability provoked by the severe pruritus and that the rigidity is not myotonic in origin. Quinine hydrochloride and prostigmine had no effect, and a myographic reading showed no evidence of repetitive discharge. The abnormal posture and hypertonicity were rapidly reversed after several days of treatment with biotin concentrate and biotin-rich foods. Roentgenograms showed no evidence of disease of the bone, and after administration of biotin the spinal curvature promptly disappeared.

PRICE, Philadelphia.

DENSITY STUDIES ON AMPHIBIAN EMBRYOS WITH SPECIAL REFERENCE TO THE MECHANISM OF ORGANIZER ACTION. MORDEN G. BROWN, VIKTOR HAMBURGER and FRANCIS O. SCHMITT, J. Exper. Zool. **88**:353 (Dec.) 1941.

Determinations of the densities of prospective neural tissue from embryos of three species of Amblystoma and Rana palustris were made by dissecting out the desired tissue and observing its rate of rise or fall in a solution of known density. There was little change in density during the cleavage, gastrulation or neurulation stages. This is interpreted as evidence that there are but slight changes in volume or water content of the prospective neural cells during the formation of the neural plate and tube. It is suggested that elevation of the neural plate and the movements of cells in the process of folding of the plate may be attributed to changes in the interaction of the molecules in the surfaces of adjoining cells. An increase in the intercellular cohesion or "attraction" between the limiting envelopes of ectodermal cells may account for an increased area of contact between cells.

WYMAN, Boston.

EXPERIMENTAL CEREBRAL CONCUSSION. D. DENNY-BROWN and W. RITCHIE RUSSELL, Brain **64**:93, 1941.

Cerebral concussion is a transient traumatic disturbance of the central nervous system which may lead to complete recovery or to death without detectable anatomic lesions. Denny-Brown and Russell studied this condition experimentally in animals subjected to head injury of known intensity produced by the measured blow of a hammer to the occipito-parietal area.

Whereas ordinarily loss of consciousness should be considered the criterion of concussion, in experiments with anesthetized animals this is not possible, and the criteria used were the following evidences of short-lasting but profound nervous disturbance: (1) loss of the corneal reflex; (2) loss of the pinna reflex; (3) marked change (rise) in blood pressure; (4) lasting inspiratory spasm, and (5) changes in muscle tone and reflexes.

In an experiment with an unanesthetized monkey these changes were observed to parallel the immediate, but transitory, unconsciousness usually called "concussion." In this "experimental concussion" there is interference with brain stem reflexes, lasting up to ninety seconds and terminating either in death or in recovery within five minutes. It is unaccompanied by any gross or microscopic intracranial lesion or by any significant change in intracranial pressure.

The blow required to produce this condition has a definite threshold. The object striking the freely suspended head must be traveling at a velocity of at

least 25 feet (7.6 meters) per second. It is the sudden acceleration (or deceleration) of the head at about 48,000 feet (1.5 kilometers) per second per second which produces the injury. If the head was prevented from moving at the moment of injury, concussion could not be produced.

The effects of such a blow as seen in normal anesthetized preparations may be summarized as follows: (1) loss of the pinna and corneal reflexes with movements of the vibrissae, indicating stimulation as well as paralysis; (2) immediate, sudden rise in blood pressure accompanied by peripheral vasoconstriction, indicating stimulation of the vasomotor center; (3) secondary, gradual fall in blood pressure, eventually leading to rapid vascular collapse and death, due to stimulation of the vagoglossopharyngeal reflex and the development of primary surgical shock unopposed by normal vasomotor reflexes; (4) sudden respiratory arrest due to stimulation of the respiratory center and loss of reflex respiratory activity, and (5) sudden flexor spasm of muscles, followed by diminished tendon jerks and abolition of the crossed extensor reflex.

Thus, in each instance concussion is characterized by stimulation of the medullary centers, accompanied by reflex paralysis of these same structures. It is suggested that the same condition exists throughout the central nervous system.

A crushing injury of the head, with depressed fracture, produces a sudden rise in intracranial pressure. Regardless of the site of injury, this type of trauma produces damage to the medulla and upper cervical portion of the cord by plunging these structures through the foramen magnum.

The authors conclude that concussion is a generalized reversible "molecular reaction" induced by physical stress. It results first in excitation, later in excitation and reflex paralysis and finally in reflex paralysis alone. It is not secondary to contusion, which results from physical stress on the supporting vascular structures, nor is it due to increased intracranial pressure or to cerebral edema.

MASLAND, Philadelphia.

CEREBRAL ELECTRICAL CHANGES IN EXPERIMENTAL CONCUSSION. DENIS WILLIAMS and D. DENNY-BROWN, Brain **64**:223, 1941.

The electroencephalogram of lightly anesthetized cats was recorded through dural leads during and after cerebral concussion produced by a hammer blow on the occiput.

Immediately after the injury, concomitant with the reflex paralysis which occurs, there is diminution or absence of electrical activity, affecting particularly the fast potentials. Abnormally slow waves, indistinguishable from those recorded in man, appeared at an inconstant interval (twenty-five to two hundred and five seconds) after the injury. In some instances they disappeared within ninety minutes; in others they persisted for long periods, depending on the severity of the injury. Similar changes were observed locally after a focal injury to the brain at the recording electrode.

The temporary diminution of electrical activity is associated with the general diminution in reflex activity occurring in cerebral concussion. The delayed development of slow waves may represent a stage in recovery from this condition.

MASLAND, Philadelphia.

DISSOCIATION AND REORGANIZATION OF CEREBRAL FUNCTION. B. SCHLESINGER, Confinia neurol. **4**:14, 1941.

Schlesinger reports the case of a patient who had constructional apraxia, confined to the left upper extremity. She was unable to construct or draw simple patterns or to imitate postures with the left arm and hand. On the basis of this case study Schlesinger concludes that the activities of the parieto-occipital region are characterized by a high degree of dissociability. Lesions may result in loss of ability to carry out certain acts while other closely related performances remain

intact. Various performances may be involved, in almost any combination, regardless of the time of acquisition and the degree of automatization.

Apart from the site and size of lesions which give rise to the phenomenon of selective elimination, dissociation may be due to the scattered arrangement of the nervous substrates which underlie the various performances, the varying functional characteristics of the involved areas, the presence of collateral innervation and individual variations in psychic organization.

If the lesion is not too extensive, disintegration of function in the parieto-occipital cortex is followed by reintegration, the structural basis for which are the equipotentiality and the collateral organization of the cortex.

DEJONG, Ann Arbor, Mich.

Psychiatry and Psychopathology

THE CLINICAL DIFFERENTIATION OF SENILE AND ARTERIOSCLEROTIC PSYCHOSES. D. ROTHSCHILD, Am. J. Psychiat. **98**:324 (Nov.) 1941.

Rothschild studied 31 cases of senile dementia verified at autopsy and 29 cases of similarly proved arteriosclerotic psychoses. Pathologic studies showed mixtures of the two forms to be more common than pure forms. Analysis of the material revealed differences in the clinical features of the two types. In patients with senile dementia the onset was later and the course longer. The onset tended to be more insidious in this type, and precipitating factors were of greater importance. Patients with arteriosclerotic psychoses usually showed one or more of the following features: headache, dizziness, syncopal attacks, seizures, symptoms of cardiac decompensation and apoplectiform attacks. Among the arteriosclerotic patients subjective complaints, depressions with suicidal tendencies and uncontrollable outbreaks of weeping and laughter were distinctly more frequent than among the patients with senile psychoses, whereas well elaborated and persistent delusions occurred only among patients with senile dementia. Intellectual impairment in the senile patients became slowly but steadily more marked, whereas in the arteriosclerotic patients the course was more rapid and included sudden episodes of confusion. Rothschild stresses the importance of cardiac involvement in arteriosclerotic psychoses. Almost half of his patients had outspoken attacks of cardiac dysfunction. Evidence of peripheral vascular disease was present in both groups, there being no statistically significant difference between the two. Rothschild concludes that the diagnosis of senile and of arteriosclerotic psychoses is made too frequently, the most common source of error being the failure to recognize toxic or symptomatic psychoses.

FORSTER, Boston.

A PSYCHOANALYTIC STUDY OF A FRATERNAL TWIN. DOUGLASS W. ORR, Psychoanalyt. Quart. **10**:284, 1941.

Orr presents data from the analysis of a fraternal twin of middle age who showed acute maladjustments and addiction to alcohol and drugs. In childhood he had been a good, conforming child, in contrast to his brother, who had temper tantrums. His psychic conflicts were as follows: 1. He tried to be like his twin because if he excelled his twin he felt anxious lest the latter be hostile. If his twin excelled him he felt hostile and was anxious because of his hostility. 2. He tried to obtain love and approval from his parents by trying at one time to be like his twin and at others to be entirely different from him. This secondary conflict was the result of his struggle between being an individual (with an individual ego) and being a twin (his ego being fused with that of his twin) and his struggle between his unique inherited potentialities and an environment that accentuated the similarities between the twins. Orr believes that these conflicts could have been avoided if the parents had minimized the similarities and emphasized the differences between the two boys.

PEARSON, Philadelphia.

THE STATUS OF THE EMOTIONS IN PALPITATION AND EXTRASYSTOLES, WITH A NOTE ON THE EFFORT SYNDROME. MILTON L. MILLER and HELEN V. MCLEAN, Psychoanalyt. Quart. **10**:545, 1941.

Miller and McLean summarize the literature on the status of the emotions in persons who show a disordered action of the heart and present material from the analysis of 4 patients, 3 men and 1 woman, suffering from palpitation and extrasystoles. During the analysis, the cardiac disturbances appeared when the defenses had been worked through and the strong, competitive urges toward the parent of the same sex began to appear in the conscious. These urges had been suppressed because the patient wished to avoid a struggle with the parent of the same sex because of love for the parent, to which he submitted. The competitive drives were blocked by a sense of guilt, which caused the patient to identify himself with the parent's symptoms, 3 of 4 of whom had heart disease. The drives, moreover, constituted a threat to the patient's desire to be dependent and aroused a fear of the loss of the parent's love.

PEARSON, Philadelphia.

THE PHYSIOLOGY OF BEHAVIOR AND THE CHOICE OF NEUROSIS. THOMAS M. FRENCH, Psychoanalyt. Quart. **10**:561, 1941.

French discusses the well established observation that a dream may indicate the onset of a somatic symptom, or even organic disease. He cites in detail a case in which the patient after a dream depicting muscular activity on the part of the dreamer's mother had lumbago and a stiff neck. He traces the physiologic pattern as follows: The patient probably had an erection during the night because of sexual activity stirred up by the analytic situation. He felt guilty about this and had the impulse to beat himself. He changed the muscular activity to seeing, as demonstrated by the fact that in the dream he saw his mother beating an iron rod. He also cites 3 cases of headache, in all of which the dreamer was involved in a conflict which might have led to motor discharges. Instead, the patient distracted the energy from the motor discharge and turned it into intense, intellectual activity, and the headaches resulted.

French believes that these cases illustrate pathologic exaggeration of the normal alternations between motor activity and thinking. In many psychosomatic symptoms there is a specific pattern of distribution of physiologic excitation which can be traced by a reconstruction of the dream work.

PEARSON, Philadelphia.

THE RORSCHACH METHOD AS A MEANS FOR THE DETERMINATION OF THE IMPAIRMENT OF ABSTRACT BEHAVIOR. DOUGLAS M. KELLY, Rorschach Research Exchange **5**:85 (April) 1941.

In 1924 Goldstein and Gelb described changes in behavior occurring in patients with organic disease which they characterized as impairment of the capacity for abstract behavior. The normal adult is able to respond in either an abstract or a concrete fashion, while the person with an organic disturbance responds almost entirely in a concrete way. This concrete attitude is more realistic and is directly determined by momentary sense impressions. The patients have no principle of classification such as is formed in categoric behavior.

Vigotsky, using a different type of test, found that the mental changes in schizophrenia were in many cases similar to those observed by Goldstein and his associates. He expressed the belief that the impairment in concept formation, although not concerned with etiology, was the main psychologic disturbance in schizophrenia. This was verified by Hanfmann and Kasanin, who added that normal persons showed the greatest capacity for abstract behavior, schizophrenic persons performed variably and patients with organic disease presented the greatest impairment in abstract thought. Normal subjects when retested could always remember the answers, but patients could rarely complete the test even after a thorough explanation of it. The authors also showed that the impairment

of conceptual thinking may be prominent in some cases of schizophrenia and not in others, whereas it is generally present among all patients with organic cerebral lesions.

Klopfer's "testing the limits" is a procedure in which, after the inquiry is completed, the patient is told that there are certain other responses which would occasionally fit and that it is of interest to know what he thinks about them. The popular and commonly seen forms are mentioned. The patient is told that some persons see certain figures or forms on the indicated card and is asked if he can find them. Sometimes he can find the obvious but not the complex forms. Those which he did not see are outlined. In almost every case he is unable to locate and accept the outlined form in place of his conception, even if it is far more obvious. This is a definite indication of impairment of abstract behavior. "If present, it points almost pathognomonically to organic intracranial damage or to a schizophrenic process."

MARCOVITZ, Philadelphia.

Diseases of the Spinal Cord

PROTRUSION OF TWO INTERVERTEBRAL DISKS IN THE CERVICAL REGION. THEODORE T. STONE, ALEX J. ARIEFF, LEO KAPLAN and C. BROWN, J. Nerv. & Ment. Dis. **93**:719 (June) 1941.

Stone and his associates describe the case of a laborer aged 48 in whom a high temperature developed after working in a draft. Thereon he noticed gradually increasing coldness in the lower half of the body, with weakness of all four extremities. There was no history of trauma. Examination four months after the onset revealed weakness of all extremities, increased tendon reflexes, pathologic plantar responses and absence of cremasteric and decrease of abdominal reflexes. The thenar and hypothenar eminences were atrophic. Pain sensibility was diminished on the left below the first thoracic dermatome, but other forms of sensation were essentially normal. Examination of the spinal fluid, including the Queckenstedt test, gave entirely normal results at first, but three weeks later, after marked progression of all symptoms, there was a complete spinal subarachnoid block, with 67 mg. of total protein per hundred cubic centimeters. The body of the sixth cervical vertebra was narrow as viewed in the roentgenograms. At operation protrusion of the fifth and sixth cervical intervertebral disks was discovered.

MACKAY, Chicago.

Treatment, Neurosurgery

THIAMINE HYDROCHLORIDE IN THE TREATMENT OF TRYPARSAMIDE AMBLYOPIA. P. J. LEINFELDER and R. B. STUMP, Arch. Ophth. **26**:613 (Oct.) 1941.

The subject of tryparsamide amblyopia is a serious one to the neurologist, and any means of combating the condition must be seriously considered.

In 1939 Muncy reported 50 cases in which vitamin B_1 and vitamin B complex were administered during the course of tryparsamide therapy, and from his study of these cases he gained the impression that yeast tablets are protective against tryparsamide amblyopia. He also reported the case of a patient in whom preexisting tryparsamide amblyopia was improved after administration of yeast tablets.

To test this assumption, Leinfelder and Stump injected thiamine hydrochloride intramuscularly in large doses in patients who showed changes in the visual fields after administration of tryparsamide. They report 2 cases.

The authors conclude that the use of thiamine hydrochloride was of no value in the treatment of changes in the visual fields occurring as a result of tryparsamide therapy. Although in both cases the patients received large doses of the vitamin, the visual fields continued to undergo progressive contraction.

SPAETH, Philadelphia.

PHARMACOLOGIC SHOCK TREATMENT OF INVOLUTIONAL MELANCHOLIA. JULIUS SOLOVAY and FRANK W. SCHWARZ, J. Nerv. & Ment. Dis. **93**:443 (April) 1941.

Solovay and Schwarz report 3 cases of involutional melancholia in men aged 58, 48 and 46, respectively. None had obtained any benefit from routine hospital treatment lasting, respectively, two years, one year and six months. Insulin shock therapy was instituted in all 3 cases, in only 1 of which actual coma was produced, with definite improvement in all. The improvement was not always notable immediately after treatment but occurred most rapidly after resocialization was attempted by sending the patients home under the supervision of relatives. Solovay and Schwarz believe that insulin shock therapy is safer and more easily controlled than metrazol shock and that the results in the treatment of involutional melancholia, even without the production of deep coma, are satisfactory.

MACKAY, Chicago.

VITAMIN B AND E THERAPY IN TABES DORSALIS. SIMON STONE, J. Nerv. & Ment. Dis. **95**:156 (Feb.) 1942.

Stone points out that the treatment of tabes dorsalis has been less satisfactory than that of other forms of neurosyphilis. That this failure may be due to a neurotropic spirochete resistant to treatment is doubtful in view of the extreme rarity with which organisms have been demonstrated in the spinal cords of tabetic patients. In various food deficiency states, such as pellagra, alcoholism, diabetes and pernicious anemia, lesions resembling those of tabes have been observed in the posterior columns. In experimental animals similar lesions have been produced by diets deficient in vitamin B complex and vitamin E. Although dietary deficiency has not been demonstrated in cases of tabes, various authors have reported subjective improvement in tabetic patients with the use of thiamine hydrochloride and vitamin E.

Stone reports on the use of oral vitamin therapy (Vegex, cod liver oil, liver extract, thiamine hydrochloride) in a group of tabetic patients receiving fever and arsenical treatment. The patients were better able to tolerate treatment. Since some patients failed to maintain the improvement noted, the intraspinal administration of thiamine hydrochloride was added to the other measures. Thirty to fifty milligrams of thiamine hydrochloride diluted in 5 cc. of fresh spinal fluid was injected slowly into the spinal canal at five to seven day intervals for one to five treatments. Improvement appeared in five to seven days, with reduction in the ataxia, urinary incontinence and frequency and severity of lightning pains. Improvement in visual acuity was observed. The intraspinal administration of thiamine hydrochloride as a safe and effective substitute for arsphenaminized serum is suggested.

Four patients without improvement under routine and fever therapy were treated with vitamin E. All showed improvement, especially when vitamin B complex was added. In general the improvement with intraspinal and combined therapy was greatest in patients with disturbances in gait, bladder difficulties and visual complaints. Gastric crises were reduced but not eliminated. Objectively, vibration sense reappeared in several cases.

Stone suggests that the lesions of tabes may be due to the effects of superimposing a deficiency of vitamins B complex and E on the neurosyphilis. Similarities are pointed out between tabes and the alcoholic myeloencephalopathies, which have been thought to be due to deficiency in the vitamin B complex. Stone believes that the vitamin B complex and vitamin E may have a synergistic action and that vitamin E may have a function in maintaining or restoring normal myelination.

CHODOFF, Washington, D. C.

VITAMINS E AND B_6 IN THE TREATMENT OF NEUROMUSCULAR DISEASES. L. M. EATON, H. W. WOLTMAN and H. R. BUTT, Proc. Staff Meet., Mayo Clin. **16**:523 (Aug. 13) 1941.

The authors report further results in the treatment of neuromuscular disorders with vitamins E and B_6. A previous report by Shelden, Woltman and Butt indicated no results in the treatment with vitamin E of 6 patients with amyotrophic lateral sclerosis, 4 with progressive muscular atrophy and 8 with progressive muscular dystrophy. The patients whose cases formed the basis of the previous report are included in the present series, having received more prolonged and vigorous treatment, and, in addition, the authors report on an additional 5 patients with amyotrophic lateral sclerosis, 1 with progressive muscular atrophy and 1 with progressive muscular dystrophy, 1 with muscular atrophy of the Charcot-Marie-Tooth type and 1 with localized panatrophy. The total series consisted of 11 patients with amyotrophic lateral sclerosis, 5 with progressive muscular atrophy, 9 with progressive muscular dystrophy, 1 with muscular atrophy and 1 with localized panatrophy. The patients with amyotrophic lateral sclerosis were treated for periods ranging from six weeks to eleven and a half months. Those with progressive muscular atrophy were treated from four to ten months and those with muscular dystrophies from five and a half to nine months. The authors state: "At the time of completion of our study, no patient who had amyotrophic lateral sclerosis or progressive muscular atrophy was known definitely to have been benefited." Four patients who had muscular dystrophy wrote that they had improved, but examination of 2 of them revealed this improvement to be subjective only. The authors state finally: "We have found no conclusive evidence that vitamin E alone or in combination with B_6 or other vitamins is of benefit in amyotrophic lateral sclerosis, progressive muscular atrophy or progressive muscular dystrophy."

ALPERS, Philadelphia.

TREATMENT OF OBSTRUCTIVE HYDROCEPHALUS IN ADULTS. JAMES C. WHITE and JOST J. MICHELSEN, Surg., Gynec. & Obst. **74**:99 (Jan.) 1942.

Treatment of hydrocephalus falls into three categories, namely, removal of the cause of obstruction, reduction of output of cerebrospinal fluid and establishment of a new channel to permit the fluid to escape from the ventricular system and to reach areas of absorption in the subarachnoid space. The cases reported by White and Michelsen were those of inoperable tumors of the third or fourth ventricle or stenosis of the aqueduct of Sylvius.

The disadvantages of former methods were numerous. Puncture openings in the callosum did not remain open; opening the anterior wall of the third ventricle often necessitated cutting one optic nerve, and coagulation of the choroid plexus was not satisfactory in adults.

A method which is much more satisfactory has been described by Stookey and Scarff. This operation is performed through a frontoparietal bone flap, the frontal lobe elevated and the bulging lamina terminalis punctured and spread open.

The other method, known as the Torkildsen operation, is performed by making a suboccipital craniectomy. The dura is opened and the arachnoid incised longitudinally. Next, a trephine opening is made over the posterior horn of the right lateral ventricle. A trocar is then inserted into the ventricle, and through it a no. 8 soft rubber catheter is placed in the ventricle and the catheter sutured to the galea, a tunnel made and the end of the catheter placed in the cisterna magna and sutured in place. The latter method is the one preferred by the authors, since it also permits exploration of the posterior fossa. Closing of the tube by adhesions of the arachnoid has not been troublesome. Seven patients have been saved by this method, 4 of whom have returned to work and remain in good condition after intervals of eighteen months to three years.

GOTTEN, Memphis, Tenn.

Special Senses

OPTIC NEURITIS CAUSED BY A COAL TAR HAIR DYE. MOSES KESCHNER and VICTOR H. ROSEN, Arch. Ophth. **25**:1020 (June) 1941.

In earlier years ocular manifestations of poisoning by various forms of cosmetics, and even drugs used therapeutically, were not uncommon. Bilateral optic neuritis as the result of the use of a coal tar hair dye is uncommon. It is especially interesting in the case reported, since the preparation bore the label: "This product must not be used for dyeing the eyelashes and eyebrows. To do so may cause blindness."

Various forms of dermatitis as a result of aniline dyes have been frequently reported. These include blepharoconjunctivitis, keratitis and various less circumscribed types of ophthalmitis. Toxic optic neuritis is an unusual result of aniline dye poisoning.

The substances most frequently employed in coal tar hair dyes are paraphenylenediamine, metaphenylenediamine, aniline and pyrogallol.

The mechanism of the production of the neuritis in the case reported was probably direct absorption of the dye through the skin, with generalized intoxication. The outstanding factor of clinical importance and interest in the case is the initial, erroneous diagnosis of tumor of the brain, but this was discarded after a history of the application of a coal tar dye three days prior to the onset of symptoms had been obtained. In the authors' case a picture similar to that of choked disks was presented.

SPAETH, Philadelphia.

RETINAL HEMORRHAGES IN THE NEWBORN. HUGH SPENCER MCKEOWN, Arch. Ophth. **26**:25 (July) 1941.

Systematic study of the fundi of large numbers of newborn infants has left no doubt as to the frequency of hemorrhages from the retinal vessels. McKeown studied a series of almost 500 infants, the majority of whom were seen within forty-eight hours after birth. Retinal hemorrhages were found in 42.1 per cent of the infants examined.

Most common were small, flame-shaped hemorrhages, superficial to the vessels; less common were thin, sheetlike hemorrhages in the nerve fiber layer, and least common were dull red, dense, diffusely round hemorrhages. The flame-shaped and the sheetlike hemorrhages are believed not to cause any subsequent impairment of vision, but the location of the dense, round hemorrhages in or near the macula and their persistence may make them a cause of permanent visual damage. Edema of the disk and commotio retinae were found frequently and usually disappeared within the first forty-eight hours.

There was positive correlation between the incidence of retinal hemorrhages and that of such abnormalities of birth as forceps delivery, breech presentation, protracted labor, cord strangulation and an unfavorable position of the head on entering the birth canal. All babies born by cesarean section, however, were free from hemorrhages.

Extensive hemorrhages occurred in 2 infants born with unusual complications: 1 with a true knot in the umbilical cord and 1 with a prolapsed cord. Hemorrhages into the vitreous were noted in 3 cases and were so extensive in 1 case that details of the fundus were obscured.

SPAETH, Philadelphia.

APLASIA OF THE OPTIC NERVE. HAROLD G. SCHEIE and FRANCIS HEED ADLER, Arch. Ophth. **26**:61 (July) 1941.

Aplasia of the optic nerve is a congenital anomaly rarely seen except in grossly malformed eyes. In fact, Cords (Einseitige Kleinheit der Papille, *Klin. Monatsbl. f. Augenh.* **71**:414-418, 1923) stated that it was one of the rarest of congenital malformations.

Aplasia of the optic nerve may occur from two sources, because the optic nerve arises from mesoderm and from neural ectoderm. The paraxial mesoderm

first grows into the fetal fissure, laying down the hyaloid vessels and connective tissue. The fetal fissure then closes from the rim of the optic cup to the hyaloid vessels, the site of the future optic papilla. If the mesoderm fails to enter the fissure complete closure may occur, preventing subsequent growth of nerve fibers into the optic stalk after they develop from the ganglion cell layer of the retina. This results in true aplasia, or complete absence of the optic nerve, not even the central vessels being present.

If development has proceeded normally except for failure of development of the ganglion cell layer of the retina, the optic nerve head, though small because of the absence of nerve fibers, should be present, as evidenced by the central vessels. Such an optic nerve head is seen clinically in well developed eyes, and in the case reported the condition was bilateral. The condition must be differentiated from atrophy of the optic nerve.

SPAETH, Philadelphia.

OPHTHALMIC ASPECTS OF ACUTE OXYGEN DEFICIENCY. R. A. MCFARLAND, J. N. EVANS and M. H. HALPERIN, Arch. Ophth. **26**:886 (Nov.) 1941.

The human eye may manifest marked alteration in any of its functions when the supply of oxygen is inadequate. The brain is most sensitive to anoxia, especially the cerebral cortex. Irreversible changes are found in the cortical tissue if it is deprived of oxygen for more than five to eight minutes, as compared with other parts of the brain and spinal cord, in which irreversible changes do not occur when anoxia is continued for as long as twenty to thirty minutes. This is in contrast to the survival time for smooth muscle tissue, for instance, which may be hours. Since the retina is essentially an extension of the brain and resembles it both histologically and functionally, one might expect the retina to be especially sensitive to oxygen deprivation.

The authors' investigations were based on a study of the following functions: (*a*) visual sensitivity, including light sense and dark adaptation; (*b*) differential sensitivity of visual intensity; (*c*) visual, that is foveal, acuity; (*d*) peripheral and central visual fields; (*e*) color vision; (*f*) after-images; (*g*) flicker fusion frequency; (*h*) intraocular tension; (*i*) extraocular muscle balance; (*j*) accommodation and convergence, and (*k*) coordinated ocular movements.

Their observations may be tabulated as follows:

The minimum, absolute threshold for light is impaired. Dark adaptation is impaired.

Visual acuity (foveal) is decreased in dim light but is practically unaffected in bright light.

The central visual fields are decreased by widening of the angioscotoma.

Color vision is apparently further impaired if it is abnormal prior to anoxia.

The latent period of the after-image is prolonged.

The diameters of the arteries and of the veins in the fundi are increased about one eighth.

Weaknesses of the extravascular muscles become significantly exaggerated.

The range of accommodation is decreased.

The ocular motor reactions, such as those employed in reading, are less orderly, and latent defects become apparent.

There is a diminished precision in fixating on test objects, and motor anomalies become accentuated.

SPAETH, Philadelphia.

Encephalography, Ventriculography, Roentgenography

SKULL LAMINAGRAPHY. BERNARD S. EPSTEIN, Radiology **38**:22 (Jan.) 1942.

Laminagraphy is a procedure by which predetermined layers of a structure may be visualized roentgenographically. It is also termed "tomography," "stratigraphy"

and "planigraphy." Epstein reports a study of normal patients and those with intracranial diseases. An attempt was made to fix the regions which might be best studied routinely. The results were compared with lateral stereoroentgenograms and anteroposterior and posteroanterior views of the skull of the same patients. The apparatus used was that devised by Alexander, which has the advantage of being readily adapted to standard equipment at slight expense.

The bony detail in laminagrams is inferior to that in ordinary roentgenograms. Only a thin layer of tissue is in critical focus, the remainder of the structure being blurred.

Laminagrams of the skull were made in the lateral projection at depths of 2.5, 5 and 7.5 cm. In most instances the 7.5 cm. plane corresponded to the center of the skull. The patients were all adults.

At a depth of 2.5 cm. the following structures are visible: 1. The frontal fossa, formed by the orbital plate of the frontal bone. This is usually concave; its anterior portion is higher than its junction with the lesser wing of the sphenoid bone. Structures in the same plane, such as the zygoma and a portion of the antrum, are also seen. 2. The middle fossa, formed by the great wing of the sphenoid and the temporal bone. The temporomandibular joint, the styloid process and the external auditory canal can be seen, and occasionally the condyle of the mandible is visualized. 3. The occipital fossa, formed by the occipital bone, which is usually thinner at this level than at deeper ones.

At the 5 cm. level the following structural differences are observed: 1. The frontal plate, forming the roof of the orbit, is somewhat thicker than at the 2.5 cm. plane. It has a straight or convex appearance, slanting down from its anterior portion to its termination in the lesser wing of the sphenoid bone or the anterior clinoid process of the sella turcica. 2. Just beneath the frontal plate the septum of the ethmoid cells are seen. The orbit is cut through, and the maxillary and frontal sinuses are cut longitudinally. 3. The middle fossa is narrower than at the 2.5 cm. level. The petrous portion of the temporal bone can be seen in cross section, and in some of the films the internal auditory meatus and the mastoid cells are visible. 4. The posterior fossa is visualized.

At the 7 cm. depth the following structural relations appear: 1. The cribriform plate replaces the frontal plate in the frontal fossa. The density of this shadow is less than that of the frontal plate, and interruptions in its continuity, which represent perforations, are seen. 2. Beneath this plate some of the ethmoid cells are visualized. The nasal conchae and the hard palate are also seen. 3. The tuberculum sellae, the sella turcica and the posterior wall of the sella, with the cells of the sphenoid sinus just below it are visualized. The basilar portion of the occipital bone and the foramen magnum are demonstrated. The odontoid process and the anterior and posterior aspects of the first cervical vertebra can be seen. 4. The posterior fossa is cut in its middle third, and the internal occipital protuberance can sometimes be seen.

Serial sections of the skull give an excellent idea of the thickness of the cranial wall, a fact which may be very useful. The sinuses can be better seen, as well as the nasal conchae. The odontoid process, the atlanto-occipital articulation and the articulation between the first and the second cervical vertebra can be visualized with the patient's mouth closed and with a minimum amount of manipulation.

The author reports the findings in 4 cases in which the laminagraphic studies were of importance in establishing the diagnosis. These included 3 cases of meningioma and 1 case of a large osteoma. In some of these cases the conventional roentgenograms failed to give definite evidence of the character of the lesion, but the laminagram showed its true nature.

KENNEDY, Philadelphia.

Congenital Anomalies

CONGENITAL MALFORMATION OF UPPER AND LOWER EXTREMITIES IN SIBLINGS WITH DIFFERENT FATHERS. KARL O. VON HAGEN, Bull. Los Angeles Neurol. Soc. **6**:82 (June) 1941.

Von Hagen reports the case of a Negro child aged 22 months whose birth had been normal but all of whose extremities were severely deformed. There was a thumb on each hand, and on the right hand a finger was attached to a bony projection from the ulna at the wrist. On the left hand were two rudimentary fingers. The thighs were short and fixed in abduction and external rotation; the knees were poorly formed and the legs short. The feet were misshapen, and their soles pointed upward, with two toes on each foot. The deep reflexes were feeble in the upper and absent in the lower extremities.

The mother of the child had had a sister with an inverted foot. She had had 3 sons and 1 daughter by a previous union. One of the sons had deformities similar to those of the patient, and the other 2 had inversion of the feet without hypodactyly. Von Hagen believes that these deformities may have resulted from an acquired alteration in the maternal germ plasm, similar to the inherited anatomic defects observed by Bagg in the descendants of mice treated with roentgen radiation.

MACKAY, Chicago.

OLLIER'S DISEASE: REPORT OF THE FIRST CASE WITH INVOLVEMENT OF THE OPTIC NERVE. JOSEPH L. NIELSON JR., Bull. Los Angeles Neurol. Soc. **6**:104 (Sept.) 1941.

Nielson reports the case of a girl aged 17 years who had begun at the age of 3 to exhibit progressive shortening of the left leg. When she was 12 years old pain in the left shoulder was followed by inability to raise the left arm higher than the shoulder. Four months before her examination diplopia appeared, resulting from progressive ophthalmoplegia with ptosis, which soon became complete. On examination there were primary optic nerve atrophy, with great reduction of vision, nearly complete ptosis and both external and internal ophthalmoplegia on the right side. Sensation was impaired over the distribution of the first two divisions of the right trigeminal nerve, and there were weakness and atrophy of the right temporal and masseter muscles. Roentgenographic study revealed erosion of the right optic foramen. Areas of decreased density, coarsened trabeculation and small regions of calcification in otherwise clear zones were found in the ends of long bones, the scapula, the ilium and many other bones. The levels of calcium and phosphorus in the serum were normal.

Nielson identifies the condition with the dyschondroplasia of Ollier because of its nonfamilial incidence in early childhood, the shortening of the limb, the normal levels of calcium and phosphorus in the blood and the characteristic roentgenologic features. The last-mentioned changes consist of rarefactive areas in the ends of the long bones on the diaphysial side of the epiphysial line, with striping due to septums 0.5 to 1.0 cm. apart lying in the long axis of the bones. Smaller bones may also be involved. The radiopaque areas are found on biopsy to consist of dysplasic cartilage. Nielson states that his case is unique in that implication of the optic nerve has not been reported previously. The treatment is symptomatic, and the course tends to gradual improvement.

MACKAY, Chicago.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. Houston Merritt, M.D., *Presiding*

Regular Meeting, Feb. 19, 1942

Chronic Seasickness: Neurologic, Psychiatric and Naval Aspects. Lieut. Robert S. Schwab, Medical Corps, United States Naval Reserve.

The entire literature on seasickness for the last twenty-six years (to and including 1915) has been reviewed in detail. During times of stress and war little interest is evident. For example, only 9 papers were written in the ten years from 1915 to 1925. In the prosperous times from 1925 to 1930, when many people traveled, over 69 articles were written. There has been a great falling off in the literature during the last ten years, and only 1 article was written in 1941. Of the 129 articles, many are highly theoretic and others are reports of personal experiences. About a dozen are excellent. A great variety of treatments is recommended, most weight being put on atropine and related drugs or sedatives of one sort or another.

It has been estimated in statistical studies by Wendt that 40 per cent of any population group will become seasick on sudden exposure to rough weather at sea. Most of these persons will recover after two or three days of exposure to such weather. About 5 per cent of the general population are subject to severe or chronic seasickness. Since the navy personnel is a selected group, the incidence of this type of seasickness among such persons is considerably lower. The present paper deals entirely with the chronic type of seasickness.

This preliminary report describes careful neurologic, psychiatric and laboratory studies on 38 subjects with the chronic type of seasickness, all members of the naval service. Most of the data were obtained from a questionnaire, as shown in the table. For the most part the men were sent into the hospital because of their illness. Two types of seasickness emerged early in this study and all cases fell under one of these two types.

Type 1.—Constitutionally intractable seasickness. Fifteen patients with this type were studied carefully. Their histories all gave strong indication of car, train, swing, elevator and other forms of motion sickness. They showed no evidence of acquiring tolerance, even after months on the same vessel. They did equally badly on large and on small vessels and were sick in calm weather as well as in rough. They were quite unable to do any work when they were seasick and were forced to remain in their bunks or in the sick bay all the time at sea. They all showed severe loss of weight, varying from 20 to 30 pounds (9 to 13.5 Kg.), at the end of their long sea experience which was sometimes as long as six to eight weeks. They suffered from the effects of chronic acidosis, and one or two had such severe gastrointestinal symptoms that appendectomy was performed. Over half of them showed strong neurotic traits and were subject to attacks of dizziness or fainting. One half showed abnormalities in barium sulfate studies of the gastrointestinal tract.

Type 2.—Development of severe seasickness only during duty on destroyers or patrol crafts in extremely rough weather. Twenty-three patients with this type were encountered. They were usually able to get along on large vessels without trouble. They gave no history of car, train or other forms of motion sickness, and only one fifth of their number were subject to mild neurotic traits or attacks of dizziness and fainting. Little loss in weight was encountered in this group.

These men were able to do their work and were up and about most of the time, and their efficiency was only partially impaired. They had no symptoms of acidosis. One third showed abnormalities in roentgenographic studies of the gastrointestinal tract. About one third of the total number gave a history of head injury with unconsciousness. There was no relation to body type, heredity, birthplace or aural disease. Neurologic and laboratory studies, including caloric tests and electroencephalograms, gave normal results.

ILLUSTRATIVE CASES

Type 1.—A naval physician with a stable history, was assigned to a destroyer on the Atlantic in the winter months. The history gave a strong evidence of car, train and other forms of motion sickness. He was sick before the ship left the harbor and was forced to go to his bunk. Vomiting and nausea persisted for six weeks, with loss of 30 pounds (13.6 Kg.) in weight. Symptoms persisted

Comparison of the Two Types of Seasickness

	Type 1		Type 2	
No. of cases	15		23	
History of car, train, swing and other forms of motion sickness	Yes		No	
Ability to work	No		Yes	
Efficiency at sea	0 to 10%		40 to 60%	
Loss of weight	Severe		Slight	
Prognosis	Poor		Good	
Disposal suggested	Survey or shore duty		Assignment to larger ship or preventive treatment	
Psychoneurotic traits	4	66%	1	23%
Neurotic traits	6		5	
Abnormal gastrointestinal series	6		5	
Normal gastrointestinal series	4		7	
History of head injury	3		5	
Subject to attacks of fainting or vertigo	8	53%	4	17%

even after he was transferred to a battleship, and he was so incapacitated, depressed and miserable that a diagnosis of a psychosis was made and he was transferred to the hospital for treatment. There was immediate recovery of symptoms. The gastrointestinal series showed abnormalities. Other studies revealed nothing significant. He was declared constitutionally unfit for sea duty and required survey from the naval service.

Type 2.—An able seaman, with three years' excellent record on a battleship, was transferred to a destroyer in the winter, when he became seasick. The illness persisted off and on during rough weather only for five weeks. He was able to do his work in spite of vomiting, and it was only because of blood-tinged vomitus that he was sent to the hospital. A gastrointestinal series revealed nothing of significance. He lost 7 pounds (3.2 Kg.) in weight. He was transferred to a large vessel and his symptoms did not return.

COMMENT

It is believed that chronic seasickness is of two types. The first type involves a constitutional factor and seems intractable. Persons subject to this form have

a difficult time at sea regardless of the type of vessel. Persons with the second type fare better on large vessels and should be able to get along without trouble under such conditions. Men in the first group have a low efficiency at sea even in the best of circumstances (under 25 per cent), whereas those in the second group can reach an efficiency of 90 per cent on larger vessels and in quiet weather rarely fall below 50 per cent efficiency, even when they are sick. In other words, the first group is unable to work with the seasickness; the second group can.

This paper will appear in full in the *United States Naval Medical Bulletin.*

DISCUSSION

DR. MADELAINE R. BROWN: I have long wanted to try for seasickness the treatment which Dr. Talbot and I have been using for paroxysmal types of vertigo, but the opportunity has never arisen. Perhaps now Dr. Schwab might try this therapy, i. e., large doses of potassium chloride. I suppose the treatment should be started three or four days, or a week, before the patient goes on board and then be continued.

DR. JAMES B. AYER: I notice that Dr. Schwab made no mention of the various forms of apparatus used in testing for seasickness, such as the Bárány chair.

DR. WILFRED BLOOMBERG: I think it was Hill who first used benzedrine, and he drew careful distinctions between two types of seasick patients: the pale and the flushed. Has Dr. Schwab any observations on that point?

DR. SAMUEL H. EPSTEIN: Is there any evidence that sailors subject to seasickness get over their seasickness eventually, or at least get more accustomed to the sea?

DR. PAUL I. YAKOVLEV, Waverley, Mass.: Were any of these patients able to overcome their seasickness by adjusting their position to the plane or the rolling of the ship?

DR. D. DENNY-BROWN: Is there good evidence that the labyrinth has anything to do with seasickness? It has been reported that deaf-mutes are never seasick. I wonder if that is true. There are several points that suggest that the disorder is not related to labyrinthine disease. 1. Patients who are seasick do not show any nystagmus. 2. When one gets ashore after being at sea, for a few days one still has the sensation that things are moving slowly. 3. Nausea and vomiting occur as a reaction to other kinds of disorientation. The old classic psychologic experiment comes to mind: A man put on a pair of glasses that made him see everything upside down and wore them continuously for a few weeks. At first there was intense nausea and vomiting, and he had to stay in bed. Eventually he was able to see things right side up and was able to get about. But when he took off the glasses again, he had to go to bed—again with vomiting. I had a patient who, because of a fracture of the cervical part of the spine, had to have continuous traction with the usual weights and pulleys at the head of his bed. His view was limited to the ceiling and the upper parts of the walls. For two days of this treatment he was nauseated and vomited repeatedly. The cause of this disturbance was obscure until he stated that he did not seem to see things right side up. Everything appeared to be on its side. His nurse seemed to him to be walking horizontally in space. He felt dizzy and nauseated whenever anything vertical entered his field of vision. He found that if he could look through the window and see some buildings, everything suddenly turned into an upright position and the nausea ceased. I realized that the trouble was that he could not see the floor or anything on it and, lying horizontally as he was, he seemed to see the ceiling as vertical. Everything appeared upright in terms of the wall at his feet. By simply hanging a picture on that wall his sensation vanished. His disturbance seemed to be a disorientation in space. Therefore it may be that the labyrinthine factor is only one of several kinds of reactions to disorientation in space.

DR. MARY A. B. BRAZIER: I should like to ask whether Dr. Schwab is not convinced of the economic value of the chart he showed. He has differentiated between two types of seasickness. In type 1 there is a great falling off of efficiency when a man goes to sea, irrespective of the size of the vessel. In type 2 there is a falling off to only about 90 or 80 per cent on the large boats, but a great falling off on the small ones. Therefore, should not men who are seasick on medium or small vessels and who belong to type 2 be moved to larger vessels and be of more economic value to the navy?

LIEUT. ROBERT S. SCHWAB: In answer to Dr. Ayer's question, there has been considerable work with the Bárány apparatus in determining whether or not persons are prone to seasickness. Examiners even went so far as to examine passengers on the Aquitania. The experimenter never induced nystagmus, but he did produce seasickness or vomiting in many susceptible persons. He examined the ability of the subject to focus both eyes after one of these slow swings of the chair. The subject was given eight turns in one direction, with the head at a 60 degree angle and then eight turns in the other. In susceptible people he noted ocular imbalance, changes in blood pressure and vomiting, whereas in hardy sailors he observed no ill effects.

As to Dr. Brown's suggestion concerning treatment with potassium chloride, I have it in mind to try this, but as yet I have had no opportunity to carry out any therapy.

Persons with seasickness of type 1 usually get sick in calm weather. As soon as the ship left the dock some of these persons could feel themselves perspiring, salivating, etc., even when there was no actual rolling of the ship. As to why such persons are in the navy, I cannot answer. I have asked every one that question and have received different answers. Some have joined to see the world, others for travel or careers and others to avoid the draft. Some come from the Middle West and have never even seen the sea.

As to Dr. Bloomberg's question regarding Hill's division into the parasympathetic and the sympathetic type, this author expressed the opinion that one type had persistent vomiting and a slow pulse and the other dizziness, vertigo, nausea, high blood pressure and a fast pulse. The statement is hard to verify. Hill advised treating the two types differently.

As to Dr. Epstein's question, persons with the first type apparently never get over their seasickness. The only cure is the proverbial one: to get under a live oak tree. They keep on vomiting, have acidosis and suffer great loss of weight. They really have organic disease of a severe sort at the time. I had a man in my group with a history of duodenal ulcer who was very seasick. I imagine more such persons will be encountered, and they will present quite a different problem.

Dr. Yakovlev asked about adjusting the position to the plane of motion of the ship. I understand from medical officers on duty on destroyers in the Atlantic in winter that this would be a physical impossibility. The vessel is moving in all planes, and jumping up and down as well.

In reply to Dr. Brazier's comment about the economic factor, the problem has two aspects. 1. The number of extra men in the officer personnel on a small ship is limited. If two officers are ill at the same time, the efficiency of the boat is seriously reduced, whereas on a large vessel one or two would not be missed so much. 2. The economic loss, I believe, is not great. The number of such cases is small—perhaps less than 1 per cent of cases of seasickness. The reason they are coming up now in such numbers is that in peace time, when conditions are much freer, one can get away with it. Ventilation on the boats is better, and men are at sea for shorter periods.

I am most interested in Dr. Denny-Brown's remarks. The work on the labyrinth in relation to seasickness has been extensive, one noteworthy investigator being an Italian, who worked with dogs. He came to the conclusion that there was such relationship. It is difficult, in looking over the vast literature on the

subject, to come to any decision, except to say that there is no conclusive experiment with respect to conditioning. One of the patients (type 1), when told he would have to go back to his vessel, vomited in the office of the hospital.

Two other points: Persons with the first type of seasickness often complain for several days ashore of terrifying nightmares in which the ship rolls around, etc. They also acquire, particularly in the officer class, a severe reaction to the difficulty. They have the feeling that they are useless, and that distresses them. One of the psychiatric aspects is the feeling of failure, and this sometimes results in a depression. A person of hysterical type had a continuation of the symptoms in a form of neurosis, vomiting even when in port. In other words, his seasickness was turned into a frank neurosis. I might have mentioned a third type. This condition is very common on destroyers in winter, and the sickness is accompanied not by nausea and vomiting but, rather, by lassitude and indifference to tobacco, sleeplessness and irritability. It occurs only in rough weather. Whether it is related to other syndromes which occur on long voyages I do not know.

Central Autonomic Paralysis. Dr. Eugene A. Stead Jr., Dr. Richard V. Ebert, Dr. John Romano and Dr. James V. Warren.

This paper was published in full in the July 1942 issue of the Archives, page 92.

PHILADELPHIA NEUROLOGICAL SOCIETY

Robert A. Groff, M.D., *Presiding*

Regular Meeting, Feb. 27, 1942

Right Frontal Lobectomy with Bilateral Ligation of the Anterior Cerebral Arteries: Report of a Case. Dr. Temple Fay and Dr. Henry T. Wycis.

This case is presented because it brings to light three important problems for discussion, namely: (1) the symptomatology referable to frontal lobe deficit; (2) the relationship of loss of consciousness to ligation of one or both anterior cerebral arteries and, finally, (3) the control of postoperative hyperthermia when surgical intervention carries the operator near the hypothalamic temperature-regulating centers.

REPORT OF CASE

P. C., a youth aged 16, was admitted on April 7, 1941 to Temple University Hospital, in the service of Dr. Temple Fay, with the chief complaint of right frontal headache and vomiting of three months' duration. At 2 years of age he had meningitis, which left him with convergent strabismus and impaired vision in the right eye.

Examination.—There was dulness to percussion over the right frontal region. The right pupil was dilated and eccentrically placed, and the reaction to light was almost absent. The left pupil was normal in size and reacted well to light and in accommodation. Vision in the right eye was reduced to the mere recognition of shadows. In the left eye the visual fields were uniformly contracted, as revealed by the perimetric charts. The fundi showed bilateral primary optic atrophy, with greater involvement on the right side. There was convergent strabismus, involving mainly the right eye. Weakness of the left side of the face of central type was the only other symptom referable to the cranial nerves. The knee and ankle jerks on the left side were slightly more active than those on the right. Coordination tests were performed on the right side only a trifle better than those on the left. Fine tremors were noted in both hands. Sensory tests for all modalities were normal.

Roentgen examination of the skull revealed a large calcified lesion in the right frontal lobe, probably an oligodendroglioma.

The patient was cooperative, but was retarded in his progress in school primarily by his poor vision. He seemed oblivious to the gravity of his situation and did not appear concerned about the fact that he was to undergo a major operation.

Operation.—On April 17 a right frontal osteoplastic flap was elevated by Dr. John Taeffner. The dura was reflected, revealing a large greenish, vascular area covering the right frontal pole of the brain. Biopsy revealed that the tumor was an oligodendroglioma, and it was decided that the lesion was inoperable. The bone flap was replaced.

Course.—The patient seemed in good health for about two months, when severe headaches returned and he was readmitted to the neurosurgical service on June 12.

Second Operation.—The tumor mass lay anterior to a point approximately 4 cm. in front of the rolandic fissure and vein. An immediate approach was made through the cortex toward the midline in order to separate the mesial aspect of the frontal lobe. The right frontal branch of the anterior cerebral artery was encountered and clipped. After establishing the posterior limits of the tumor, the dissection of the frontal lobe was carried laterally so as to encounter the wing of the sphenoid bone. Several large branches from the middle artery were secured by silver clips and sectioned, and the tumor mass was mobilized along the wing of the sphenoid, carrying the dissection downward and forward. The tumor was observed to have extended under and through the falx to the opposite side, and a large mass of tumor tissue, about the size of half an orange, was removed from the left frontal lobe after opening the falx and securing the left anterior cerebral artery. The tumor was then freed from the region of the cribriform plate and the anterior clinoid processes, and, with final securing of the anterior branch of the anterior cerebral artery, the neoplasm and the entire right frontal lobe were removed. The patient could be aroused at the end of the operation and throughout its course, even after both anterior cerebral arteries were ligated.

Course.—Immediately after operation the rectal temperature rose to 105 F., with concomitant increase of the respiratory and pulse rates. He was immediately placed on a refrigeration blanket and the hyperthermia controlled. Recovery was gradual, and within three weeks he had returned to his preoperative neurologic status.

On November 17 Dr. O. S. English reported on the patient's psychiatric status. "This patient's intellectual capacity remains the same as on the first examination (eleven days after operation). Today his face has lost its serious, restrained look. I should not say that this lack of affect or diminution in normal anxiety is so serious as to interfere with the boy's taking up some work in a trade school and learning something which would be of economic value to him. Certainty, at present he reasons well and could follow instructions, even though he might be somewhat lacking in initiative."

DISCUSSION

DR. O. S. ENGLISH: I saw this boy only after the operation, not before. When one encounters loss of tissue in the frontal lobe of the brain one expects some changes in personality. I think there have been some such changes in this patient, but probably rather slight. A practical question is whether any more will follow. When I first saw him in the ward, he seemed to have a normally serious expression, was alert, polite, a little aloof perhaps, and yet as respectful as one would expect a well brought up boy to be. When I saw him the next time, in about a week, he had undergone a decided change. He had a rather constant smile on his face and a twinkle in his eye, and from that time he was childishly facetious and treated all subjects lightly. He tells me tonight that he goes to school, makes good grades and gets there and back by himself.

Since the operation he is regarded as being more friendly. He has made more friends, and people have commented on the fact that he has changed in this respect.

I suppose from the practical standpoint, as well as from the point of view of mental hygiene, one ought to make sure that this boy's parents, his teachers and any others interested in him keep before him the need of a concrete plan of life, more than one would ordinarily do with an adolescent who had not undergone the loss of tissue that he has.

In thinking of this case in relation to work by Drs. Freeman and Watts, with which all are familiar, it will be recalled that these surgeons produced favorable changes by destruction of frontal lobe tissue. Patients with a lesion such as this patient had are too anxious, too concerned about unimportant and unconstructive ideas. In the case of a normal adolescent in which something destroys tissue and interferes with normal feeling and ideation, the problem is different.

DR. HENRY T. WYCIS: The vision the boy has now enables him to recognize only a mere shadow in the right eye. In the left eye he has fairly normal vision. He is able to get about the streets and to make his own way on the streetcars without trouble.

DR. TEMPLE FAY: The fact that the boy has not lost as much mentality as one might expect from a resection of the frontal area may be explained by gradual compensation in the blood supply, possibly because of the slow-growing tumor, whereas the sudden removal of the blood supply of the anterior cerebral artery in an older person might produce another picture.

I have always been under the impression that "consciousness" was an attribute of many areas of the brain, and not confined to one artery or zone, as Dandy has contended. The failure of his patients to recover can be traced to long periods of low blood pressure on the operative table.

Cysticercus Infestation of the Brain: Report of a Case. DR. RALPH MELORO and DR. SAMUEL B. HADDEN.

This case is presented because of the sudden onset of serious symptoms, with fairly rapid fatal termination. The patient, a Slavic woman of 45, was taken ill the evening before admission to the hospital and rapidly passed into coma. The clinical diagnosis was suspected brain tumor, diffuse cerebral edema, cerebral hemorrhage and cardiovascular disease with hypertension.

The final histologic diagnosis was a cysticercus lesion in the fourth ventricle, only the solitary cerebral cyst being observed.

Surgical treatment is debatable but is justified when the symptoms are focal. The outlook is grave in cases of multiple infestation with Cysticercus cellulosae. In determining the course of epileptiform convulsions, diagnostic measures to ascertain the presence of Cysticercus might well be included. Careful palpation and possibly roentgenographic studies to locate calcium deposits in skeletal muscles are more informative than various cutaneous and complement fixation tests.

DISCUSSION

DR. HELENA E. RIGGS: It is remarkable that there have been 3 cases of this kind in the laboratory of the Philadelphia Hospital in the past three years, in all of which the organisms were apparently living. One was the case presented tonight. In the second case Dr. Groff operated for tumor of the posterior fossa, and the parasite was found in the material taken for biopsy. The finding was so unexpected that the true nature of the lesion was discovered only after consultation with Dr. H. M. Dixon, of the department of histopathology. The third case was that of a girl with cerebellar abscess. Living cysticerci were seen in the diaphragm and the psoas muscle in tissue taken post mortem. No parasites could be demonstrated in or around the abscess, but what appeared to be calcified organisms were present in the choroid plexus. The case Dr. Meloro and Dr. Hadden have

presented is unusual in that there was no evidence of meningoencephalitis. I am told, however, that such an inflammatory reaction occurs only when the parasite is dead. The clinical symptoms in this case suggest that the encysted parasite, which was very loosely attached to the choroid plexus in the fourth ventricle, acted as a tumor of the ball valve type. Impaction in the narrow isthmus resulted in acutely increased intraventricular pressure. In the presence of chronic vascular disease, which the patient showed, the sudden alterations in cerebral circulation so produced resulted in hemorrhages in the midline. The hemorrhages in the vegetative nuclei of the hypothalamus were undoubtedly a factor in the sudden death.

DR. R. A. GROFF: I operated in 1 of the cases reported by Dr. Riggs and have more information about the subsequent history. About six months after the patient's discharge from the Philadelphia General Hospital she entered the Brooklyn Hospital, was operated on for parasites in the cerebral hemisphere and made a good recovery. However, she was again admitted at a later date because of similar complaints. I have since lost track of her.

DR. HELENA E. RIGGS: Were the parasites dead at the time of the second operation?

DR. R. A. GROFF: The report did not state. Ventriculographic examination revealed a lesion in the left cerebral hemisphere, surgical exploration of which revealed additional parasites.

DR. J. C. YASKIN: When one thinks of cysticercus infestations, postural vertigo, more particularly the syndrome of Bruns, comes into mind. It was my impression, until this evening, that the cysticercus involves principally the structures of the posterior fossa, but the frequency of convulsions indicates that supratentorial structures are frequently implicated.

DR. F. H. LEWEY: Dr. Yaskin is quite right that in cases of cysticercus infestation of the fourth ventricle the most impressive clinical picture is produced when the vesicle is movable and the patient turns his head. However, the majority of cysticerci are observed in the meninges over the cerebral hemispheres.

DR. SAMUEL B. HADDEN: On admission this patient was desperately ill, and, with the history of treatment for hypertension over a long period and a practically normal blood pressure, it was felt that circulatory inefficiency might account for her symptoms. Within a few days she improved greatly and tumor of the brain, though under consideration, was not thought likely. There was a sudden increase in severity of symptoms, and death occurred about twelve hours after a period of complete unconsciousness.

DR. RALPH MELORO: This patient on admission was considered to be practically moribund and remained in an extremely critical condition until shortly after study of the spinal fluid, when she improved and regained consciousness. It is possible that the spinal puncture dislodged the cysticercus, permitting some restoration of cerebrospinal fluid circulation and resulting in diminution of intracranial pressure. After this lucid interval the downward course was rapid.

Tuberculoma of the Central Nervous System Simulating Tumor of the Brain or Spinal Cord. DR. GEORGE WILSON, DR. CHARLES RUPP and DR. HARVEY BARTLE JR.

Tuberculoma of the central nervous system is a not uncommon observation at autopsy, but its clinical recognition is difficult. Of 17 cases in which the signs and symptoms simulated those of an intracranial neoplasm (13 cases) or a tumor of the spinal cord (4 cases), the correct diagnosis was made clinically only once. Several factors contributed to the failure in diagnosis. Most important was the paucity or absence of evidence suggestive of an accompanying extraneural tuberculous focus. Even at autopsy extraneural tuberculous foci were not conspicuous, often being limited to a minimal healed pulmonary lesion, and in 6 cases no tuberculous lesion aside from the tuberculoma in the nervous system

could be found. Similar cases have been described by other observers. While it is possible that a microscopic tuberculous focus may have escaped detection, from the clinical standpoint the granuloma in the nervous system may be considered the only tuberculous lesion. Clinical evidence of tuberculous meningitis was present in only 5 cases and in 3 instances appeared only terminally. Studies of the spinal fluid were of no help in diagnosis. With 1 exception, all the patients were adults. In 7 of the cases of intracranial tumor operation was performed, in 2 of which the tuberculoma was successfully removed. In 1 case the patient survived twenty-one months, in the other, seven months.

DISCUSSION

DR. HELENA E. RIGGS: Critical, long term analysis of the postmortem records of a general hospital should provide valuable information for the clinician. Statistical studies from institutions dealing with selected types of cases are frequently misleading in their conclusions, since such material does not represent true random sampling. This factor, I believe, accounts for the difference in age, location, etc., in the present series of cases of tuberculoma and those reported from surgical clinics. Another fact of interest brought out by this study is the long duration of symptoms in cases of tuberculoma of the nervous system. Before these cases were analyzed, my impression was that neural involvement by tuberculoma was analogous to the metastatic involvement of the nervous system by carcinoma, a terminal neural invasion as result of a chronic and widespread visceral process. In this study, however, in 30 per cent of the cases of neural lesions there was no clinical evidence of visceral tuberculosis, and in 12 per cent no extraneural focus could be demonstrated even at autopsy.

DR. F. C. GRANT: I have seen 3 cases of tuberculoma of the central nervous system in the past five years. In 1 of these, recently reported by Dr. Weinberger from the University Clinic, the diagnosis was suggested by the roentgenographic findings prior to operation. The operative removal of this tumor from the cerebrum presented no particular difficulties. The child is still alive and in good physical condition, eighteen months after operation. In 1921 Dr. Frazier's records show that he removed a mass lesion, later proved to be a tuberculoma, from the cerebellum of a 9 year old girl. That patient is still alive and well and has raised a family.

In the past it was feared that the removal of a tuberculoma would result in tuberculous meningitis. It was suggested that such lesions were therefore better left undisturbed. The gross differentiation from meningioma or other solid tumor at operation is difficult. Certainly, in 2 cases in which recent operation was carried out the lesion was suspected of arising from the meninges. If the mass is found to be tuberculous, every effort should be made to build up the patient's resistance—plenty of sunlight, fresh air and a full diet. Tuberculous meningitis may occur as an operative complication, but certainly not as an inevitable one.

DR. R. A. GROFF: Last year it was reported from the Mayo Clinic that cerebral tuberculomas when removed are much less likely than cerebellar lesions to be the cause of widespread tuberculous meningitis. Removal of the latter is in most instances followed by tuberculous meningitis. The reason for this is that in cases of the cerebellar type the disease infiltrates the fine fissures of the cerebellum, and in removal of the lesion the surgeon invariably cuts through, rather than goes around, them. A cerebral lesion, on the other hand, is not usually incised, since it remains localized.

Neuropathologic Changes in Cases of Meningitis Treated with Drugs of the Sulfanilamide Group. DR. MATTHEW MOORE.

With the advent of drugs of the sulfanilamide group there appeared on the horizon chemotherapeutic agents which have proved to be effective in materially lowering the fatality rate of those forms of meningitis which formerly had

approached a mortality of 100 per cent, and in reducing to less than 10 per cent the fatality rate of the epidemic form of cerebrospinal meningitis. Of the drugs of this group which have been used in the treatment of the various meningitides, sulfanilamide, sulfapyridine (2-[paraminobenzenesulfonamido]—pyridine), sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) have been found most effective.

Six cases of streptococcic and pneumococcic meningitis are presented, illustrating a number of significant therapeutic problems concerned with dosage, toxicity, use of antiserums, prophylaxis in respect to infection of the paranasal sinuses, middle ear and mastoid, surgical and nonsurgical attention to foci of infection and the possible occurrence of sequelae in protracted cases of meningitis in which recovery finally occurs.

The neuropathologic studies illustrate that insufficient therapy with drugs of the sulfanilamide group in the presence of foci of infection permits the development of a chronic meningeal phase simulating tuberculous meningitis. Adequate therapy produces clearing of the meningeal inflammatory process. On the basis of the neuropathologic studies and a review of the literature, suggestions for prophylactic and active treatment are offered.

With present knowledge of the subject, in treatment of the virulent meningitides, it is better to give too much of a sulfanilamide drug and give it too soon than to give too little and give too late.

DISCUSSION

DR. G. D. GAMMON: I should like to ask Dr. Moore about the vacant spaces in the meninges. Were there accumulations of fluid which were cleared of pus cells during the treatment? Were there any large cystic collections?

DR. MATTHEW MOORE: It is obviously preferable to anticipate the possibility of meningitis and to prevent its occurrence, when possible, by the use of the sulfanilamide drugs. This applies especially to cases encountered by the otorhinolaryngologist. The drugs of the sulfanilamide group should be administered as a prophylactic measure against the complication of meningitis in cases of fracture of the base of the skull, particularly when the frontal sinus is involved, and in operations for abscess of the brain or osteomyelitis of the skull.

In answer to Dr. Gammon's question, section of the brain in the case to which he referred and in similar cases showed that the leptomeninges were loosely adherent to the brain and the subarachnoid space was dilated. Cerebrospinal fluid, rather than purulent material, escaped, and I conclude therefore, in view of the extremely high initial cell count of the cerebrospinal fluid, that in all probability the dilated subarachnoid space was filled with pus before a sulfanilamide drug was given in therapeutic amounts.

Effect of Drug Therapy on the Electroencephalogram of Epileptic Patients. DR. R. M. MASLAND and DR. DONALD SCOTT JR.

The following report is an evaluation of the response to medication of patients with focal seizures as compared with that of patients with idiopathic epilepsy. The type of the disease presented by each patient was differentiated both on clinical grounds and by means of the electroencephalogram, and a few typical cases from each group were selected for detailed study.

The term focal was applied to the form characterized by (*a*) jacksonian seizures and (*b*) abnormal cortical electrical potentials (spikes) localized to a small area and reproduceable on repeated examination.

In 8 cases of this group selected for study, standard leads (14 wires) were applied and records obtained under control conditions without medication. Studies were then made during medication with phenobarbital or dilantin and the changes in the record observed. The effect of three minutes' hyperventilation was also noted. Changes in activity were tabulated according to the average maximum size of the spike potentials from a given lead and the frequency with which an

observable spike appeared within a given period. Each recording lasted for an average of about one hour.

Study of the records of the patients with focal epilepsy reveals a fairly good clinical response to phenobarbital but only a minor reduction in the size and frequency of the abnormal electrical potentials. There was a very good clinical response to dilantin, and this clinical improvement was accompanied in many cases by nearly complete disappearance of the focal abnormality in the electroencephalogram. Little change in the frequency of focal spikes was produced by hyperventilation.

For study of the idiopathic type we selected children or young persons who showed frequent generalized petit mal seizures accompanied by bilaterally symmetric spike and slow wave episodes in the electroencephalogram. Five patients were chosen who showed very frequent episodes, as these lent themselves most readily to analysis. The method of study was similar to that for the patients with focal epilepsy. Patients with the idiopathic type obtained little or no clinical improvement from either phenobarbital or dilantin. The electroencephalograms showed absolutely no change in the size of the abnormal potentials or in the duration of each abnormal episode. Slight reduction in the frequency of the episodes was observed in 1 patient with a mild form of the disease, but this was not sufficient to be significant. On hyperventilation there was always a great increase (of from four to six times) in the frequency and duration of the episodes, without change in the size of the potentials. One patient exhibited a reduction in frequency when placed on a ketogenic diet.

These experiments show that there is a striking difference between the focal and the idiopathic type of convulsive disorder in the response to medication and in the effects of hyperventilation.

DISCUSSION

DR. F. C. GRANT: My associates and I have been sending our epileptic patients to Dr. Masland, and he tells us that not enough phenobarbital or dilantin is being given, because there are still abnormal spikes in the tracings. A much more intelligent idea of the amount of therapy necessary can be obtained if one can check it by electroencephalographic tracings.

DR. R. S. WIGTON: I should like to ask Dr. Masland whether the effect of these drugs has been noted on abnormal potentials due to other causes, such as tumor of the brain. Also, what are the effects of these drugs on the electroencephalogram of persons without epilepsy or of experimental animals?

DR. R. M. MASLAND: Dr. Scott and I have studied several of Dr. Grant's cases of tumor from this point of view. I should have mentioned in the paper that we purposelessly eliminated mass lesions in this investigation. The cases discussed are all those of small scars. The wave in a case of tumor is quite different in that it is a slow type of disturbance, and it has not shown any change on the administration of large doses of the drugs.

We have not observed particular changes in normal persons after medication, and although we have not studied a large series of normal persons in that regard, we can draw the conclusion from observations on the normal hemisphere of patients with focal spikes. If the hemisphere was normal when the patient started medication, the drug did not change the tracing much. If there was generalized disturbance, due to transmission of the abnormal activity from the affected to the normal hemisphere, as improvement in their focal lesions appeared there was also improvement in the tracing from the opposite side.

Book Reviews

Functional Neuroanatomy. By Wendell J. S. Krieg, Ph.D. Price, $6.50. Pp. 553. Philadelphia: The Blakiston Company, 1942.

The author and publisher have combined to make this book a remarkable contribution to the teaching of neuroanatomy. The material is presented from the point of view of function rather than of topography. Wherever possible, especially in the case of the sensory elements, systems are dealt with in their entirety, from origin to final termination. The higher motor levels are discussed under the headings pyramidal, extrapyramidal, autonomic, etc. The chapters on the brain stem are systematized on the basis of the cranial nerves, and the work is completed by special chapters on the cortex, rhinencephalon and cerebellum.

The book is lavishly illustrated with extraordinarily beautiful drawings and diagrams, nearly all of which were prepared by the author himself. This was necessary because ". . . a great part of the figures were to draw heavily upon a mental picture which only a person thoroughly familiar with the subject can attain. Since the only practical approach to the material itself is by means of sections, it is necessary to treat illustrations of sections in such a way that the student will build up a vivid three-dimensional picture of each system. The atlas of sectional reconstructions at the back of this book is the result of the application of this plan." The three-dimensional diagrams and fantom drawings thus resulting from the author's remarkable artistic ability aid greatly in visualizing the nervous system in terms of its interconnections.

The usefulness of the book as a teaching aid is greatly extended by the addition of an excellent laboratory manual. In this the student is directed, system by system, to procedures calculated to aid in his acquisition of the factual material on which the subject is based. At the same time, the principal functional aspects of the various systems are presented in accompanying chapters, so that the result is a well integrated exposition of neuroanatomic relations and neurophysiologic information, which is presented simultaneously with the basic dissections and study of histologic material.

An understandable determination not to confuse the student led to the formulation of "ten commandments" for textbook writing, which are presented in the preface. Close application of these principles has led to a minimal use of neurologic terminology. Controversial topics either are not mentioned or are dismissed with a word, even when the disputed points are fundamental. Bibliographic references are entirely omitted from the text, since it is the opinion of the author that "The long and uncritical bibliographies in most modern texts are used but little by the student. He is in no position to judge the validity of the methods or conclusions, and does not have time to enter into controversial subjects, however much they may interest the specialist. The advanced scholar and instructor need journal references and many of them, but they are better included in the larger or more specialized treatises."

The application of such principles has resulted in rather extreme simplifications. This is coupled with the fact that the method of treatment of diagrams and fantom three-dimensional reconstructions also tends toward dogmatic statement of factual detail. Such authoritative statements, rather than appeals for independent judgments, become all the more unfortunate when errors are committed, since the student is denied bibliographic reference to the original evidence, and in many cases is not even informed that there is a lack of agreement. Various instances of this sort occur from time to time throughout the text. In figure 167 the classic error of tracing the tail of the caudate nucleus into the nucleus amygdale, rather than into the putamen, is recommitted. On page 283 the statement is made that "the most careful of the older workers [Wilson] failed to find

corticostriate fibers," whereas nowhere can the reviewer find mention of Cajal's statement that the striatum receives extensive cortical connections. An unusually complete, but somewhat uncritical, list of connections of the red nucleus is ameliorated only by the statement that "not everyone would agree on the connections as given above."

Despite these unfortunate aspects, to which perhaps too much space has been devoted, attention should be strongly directed toward the many virtues of the book for use as a teaching manual. The clarity of exposition and the order of consideration of subject matter are admirable. The freshness of approach; the unusual, and often entertaining, illustrations, chapter initial decorations and end papers; the excellent laboratory instructions, and the correlations with physiologic phenomena should place this book high on the list of texts available for neuroanatomic instruction.

Psychotherapy in General Practice. By Maurice Levine. Price, $3.50. Pp. 306, plus index; no illustrations. New York: The Macmillan Company, 1942.

As the name suggests, this book is addressed to general practitioners. It would also be an excellent book for medical students and, as a digest of current points of view, for psychiatrists. It does not attempt to turn the average physician into a specialist; rather, it points out the indications for action; the physician's proper attitude toward difficult personal problems, such as when and when not to ask questions and when to refer patients for psychoanalysis or seek commitment.

Typical, and ably done, is the chapter on suicide. The author points out that there are many conditions besides the manic-depressive psychosis in which suicide is a real danger, and proceeds to list and describe them: the normal human being in some cultures; the hysterical psychopathic personality; delirium; alcoholism; schizophrenia and paranoid and panic states, and reactive depressions. He then lists and discusses the manifestations which point to a real danger of suicide: certain vegetative abnormalities; depressive delusions; a past history of suicidal attempts, and recovery from depression. He also describes the characteristics of suicidal threats which should probably be disregarded and suggests an attitude for the physician.

This book may be highly recommended for its purpose.